Chapter 1: Selective internal radiation therapy within the hepatocellular carcinoma multidisciplinary team

1 State of the art: hepatocellular carcinoma
   L Bolondi

7 Evidence-based integration of selective internal radiation therapy into hepatocellular carcinoma management
   B Sangro

13 Clinical studies in hepatocellular carcinoma
   V Vilgrain, M Abdel-Rehim, A Sibert & M Ronot

17 The effectiveness of selective internal radiation therapy in challenging cases of liver-predominant unresectable hepatocellular carcinoma
   P Malfertheiner, C Verslype, FT Kolligs, K Schütte, V Vandecaveye, PM Paprottka & J Rick

Chapter 2: Selective internal radiation therapy within the colorectal/ liver multidisciplinary team

29 State of the art: colorectal liver metastases
   A Sobrero & A Pastorino

33 Evidence-based integration of selective internal radiation therapy in the management of colorectal liver metastases
   HS Wasan

37 Ongoing selective internal radiation therapy-based studies in the treatment of liver-dominant metastatic colorectal cancer
   V Heinemann

41 Case histories in unresectable liver-dominant metastatic colorectal cancer
   RA Sharma, M Peeters & J Taib
## Chapter 3: Selective internal radiation therapy – downsizing and downstaging to resection and transplantation

- **49** The evidence for resection post-selective internal radiation therapy  
  B Garlipp & CJ Bruns

- **53** The safety of resection post-selective internal radiation therapy  
  F Rotellar, F Pardo & P Martínez-Ortega

- **57** Liver function considerations for post-selective internal radiation therapy resection (hepatocellular carcinoma and metastatic colorectal cancer)  
  B Sangro

- **61** Bridging and downstaging to transplantation in hepatocellular carcinoma  
  GM Ettorre, GBL Sandri, R Santoro, P Lepiane, M Colasanti & G Vennarecci

- **65** Hypertrophy in the contralateral lobe post-selective internal radiation therapy  
  DM Manas

## Chapter 4: Selective internal radiation therapy – state of the art for interventional radiologists and nuclear medics

- **69** Latest selective internal radiation therapy recommendations from EU proctors  
  G Maleux

- **73** Optimizing the use of PET with selective internal radiation therapy  
  P Flamen

- **77** Selective internal radiation therapy dosimetry  
  A Kennedy

## Chapter 5: Selective internal radiation therapy for other liver tumors

- **83** Liver metastases from neuroendocrine tumors  
  A Kennedy

- **89** Evidence-based integration of selective internal radiation therapy into the management of cholangiocarcinoma  
  L Fartoux & O Rosmorduc

- **93** Evidence-based integration of selective internal radiation therapy into the management of breast cancer liver metastases  
  R Cianni & G Pelle

- **97** Evidence-based integration of selective internal radiation therapy into the management of ocular melanoma liver metastases  
  B Stedman

## Chapter 6: Selective internal radiation therapy and other modalities for liver tumors

- **101** Cost of selective internal radiation therapy versus other modalities  
  HS Wasan

- **105** How does selective internal radiation therapy compare with and/or complement other liver-directed therapies?  
  I Bargellini
The next few decades will see dramatic changes within the field of oncology. Whilst the burden of disease is set to increase, the available armamentarium to the oncologist will be greater, more robust and offer the potential to focus on individual needs. Future Oncology provides a forum for a new era of cancer care. The journal focuses on the most important advances and highlights their relevance in the clinical setting.

Accessible 'at-a-glance' formats are important in an increasingly time-constrained clinical community. The article structure has been optimized to make information immediately understandable and accessible. Future Oncology takes a forward-looking stance toward the scientific and clinical issues, together with the economic and policy issues that confront us in a new era of cancer care. The journal includes news and views, literature awareness regarding new biomarkers, concise commentary and analysis, reports from the conference circuit and full review articles.

Coverage includes:
- Advanced computer and software systems for modeling and directing therapy
- Adverse events and drug safety
- Biological processes involved in cancer and how new understanding will impact treatment
- Cancer risk assessment
- Changing patterns of disease and new findings in cancer etiology
- Clinical implications and applications for new biomarkers
- Healthcare policy
- Impact of molecular genetics on prevention, screening, diagnosis and treatment
- Integration of diagnostic and therapeutic approaches
- New therapeutic targets
- Pharmacoeconomics and cost–benefit issues in cancer
- Profiles of new anticancer agents
- Screening programs and methodology
- Selective and personalized approaches

Subscription options

Institutional subscriptions
Future Oncology is available in print, electronic or print and electronic formats, and pricing will depend on your organization type (academic, corporate, hospital, etc). Please contact d.march@futuremedicine.com for more details. Global e-access licenses are available on request and attract considerable discounts from standard site license fees. For further details on global access licenses, please contact d.march@futuremedicine.com

Consortia pricing
Future Oncology welcomes discussion with all consortia, and offers flexible packages and discounted prices. If you have specific questions or would like a quote please contact d.march@futuremedicine.com for more details.

Personal subscriptions
Personal subscriptions are currently available to all Future Medicine journals. Payment must be made from a personal credit card registered to a home address. Print subscriptions will only be sent to a personal address. Please contact d.march@futuremedicine.com for our personal order form, or order online at www.future-science-group.com/subscriptions.

Subscription rates

<table>
<thead>
<tr>
<th></th>
<th>Print and online</th>
<th>Online</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal (16 issues)</td>
<td>£GBP 1800 € Euro 2365 $ US 2990</td>
<td>£GBP 1625 € Euro 2150 $ US 2720</td>
</tr>
<tr>
<td>Academic/hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corporate/government</td>
<td>Please contact <a href="mailto:d.march@futuremedicine.com">d.march@futuremedicine.com</a> for more details</td>
<td></td>
</tr>
</tbody>
</table>

Reprints

Article reprints are available through our reprint service. Please contact s.cavana@futuremedicine.com

Ordering information

Please contact your local sales representative to place an order:

Worldwide
Future Medicine Ltd
Unitec House, 2 Albert Place, London N3 1QB, UK
T: +44 (0)208 371 6090
F: +44 (0)208 343 2313
E: subscriptions@futuremedicine.com

North America
E: sales.us@futuremedicine.com

Latin America & the Caribbean
dotLib
T: +55 (21) 3431 3430
E: info@dotlib.com

China
Charlesworth China
T: +86 106 779 1601
E: sales@charlesworth.com.cn

Japan
USACO Corporation
T: +81 3 3505 3257
E: marketing@usaco.co.jp

Korea
Shinwon Datanet Inc.
T: +822 326 3535
E: info@shinwon.co.kr

Asia (excluding Korea, China & Japan)
Rosinda M Razi
T: +65 3153 0633
E: rrazi@futuremedicine.com

Middle East
Naseej
T: +966 1 477 0477 ext. 232
E: a.alkredees@naseej.com

AIMS & SCOPE

The next few decades will see dramatic changes within the field of oncology. Whilst the burden of disease is set to increase, the available armamentarium to the oncologist will be greater, more robust and offer the potential to focus on individual needs. Future Oncology provides a forum for a new era of cancer care. The journal focuses on the most important advances and highlights their relevance in the clinical setting.

Accessible ‘at-a-glance’ formats are important in an increasingly time-constrained clinical community. The article structure has been optimized to make information immediately understandable and accessible. Future Oncology takes a forward-looking stance toward the scientific and clinical issues, together with the economic and policy issues that confront us in a new era of cancer care. The journal includes news and views, literature awareness regarding new biomarkers, concise commentary and analysis, reports from the conference circuit and full review articles.

Coverage includes:
- Advanced computer and software systems for modeling and directing therapy
- Adverse events and drug safety
- Biological processes involved in cancer and how new understanding will impact treatment
- Cancer risk assessment
- Changing patterns of disease and new findings in cancer etiology
- Clinical implications and applications for new biomarkers
- Healthcare policy
- Impact of molecular genetics on prevention, screening, diagnosis and treatment
- Integration of diagnostic and therapeutic approaches
- New therapeutic targets
- Pharmacoeconomics and cost–benefit issues in cancer
- Profiles of new anticancer agents
- Screening programs and methodology
- Selective and personalized approaches

Subscription options

Institutional subscriptions
Future Oncology is available in print, electronic or print and electronic formats, and pricing will depend on your organization type (academic, corporate, hospital, etc). Please contact d.march@futuremedicine.com for more details. Global e-access licenses are available on request and attract considerable discounts from standard site license fees. For further details on global access licenses, please contact d.march@futuremedicine.com

Consortia pricing
Future Oncology welcomes discussion with all consortia, and offers flexible packages and discounted prices. If you have specific questions or would like a quote please contact d.march@futuremedicine.com for more details.

Personal subscriptions
Personal subscriptions are currently available to all Future Medicine journals. Payment must be made from a personal credit card registered to a home address. Print subscriptions will only be sent to a personal address. Please contact d.march@futuremedicine.com for our personal order form, or order online at www.future-science-group.com/subscriptions.

Subscription rates

<table>
<thead>
<tr>
<th></th>
<th>Print and online</th>
<th>Online</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal (16 issues)</td>
<td>£GBP 1800 € Euro 2365 $ US 2990</td>
<td>£GBP 1625 € Euro 2150 $ US 2720</td>
</tr>
<tr>
<td>Academic/hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corporate/government</td>
<td>Please contact <a href="mailto:d.march@futuremedicine.com">d.march@futuremedicine.com</a> for more details</td>
<td></td>
</tr>
</tbody>
</table>

Reprints

Article reprints are available through our reprint service. Please contact s.cavana@futuremedicine.com

Ordering information

Please contact your local sales representative to place an order:

Worldwide
Future Medicine Ltd
Unitec House, 2 Albert Place, London N3 1QB, UK
T: +44 (0)208 371 6090
F: +44 (0)208 343 2313
E: subscriptions@futuremedicine.com

North America
E: sales.us@futuremedicine.com

Latin America & the Caribbean
dotLib
T: +55 (21) 3431 3430
E: info@dotlib.com

China
Charlesworth China
T: +86 106 779 1601
E: sales@charlesworth.com.cn

Japan
USACO Corporation
T: +81 3 3505 3257
E: marketing@usaco.co.jp

Korea
Shinwon Datanet Inc.
T: +822 326 3535
E: info@shinwon.co.kr

Asia (excluding Korea, China & Japan)
Rosinda M Razi
T: +65 3153 0633
E: rrazi@futuremedicine.com

Middle East
Naseej
T: +966 1 477 0477 ext. 232
E: a.alkredees@naseej.com
Future Medicine titles endorse the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, issued by the International Committee for Medical Journal Editors, and Code of Conduct for Editors of Biomedical Journals, produced by the Committee on Publication Ethics. This information is also available at www.futuremedicine.com

Manuscript submission & processing
Future Medicine titles publish a range of article types, including solicited and unsolicited reviews, perspectives and original research articles. Receipt of all manuscripts will be acknowledged within 2 weeks, and authors will be notified as to whether the article is to progress to external review. Initial screening of articles by internal editorial staff will assess the topicality and importance of the article. Following the evaluation of a manuscript, and relevance to the journal in question, if you are interested in submitting an article, or have any queries regarding article submission, please contact the Managing Commissioning Editor for the journal (contact information can be found on our website at: www.futuremedicine.com. For new article proposals, the Managing Commissioning Editor will require a brief article outline and working title in the first instance. We also have an active commissioning program whereby the Commissioning Editor, under the advice of the Editorial Advisory Panel, solicits articles directly for publication.

External peer review: Through a rigorous peer review process, Future Medicine titles aim to ensure that reviews are unbiased, scientifically accurate and clinically relevant. All articles are peer reviewed by three or more members of the International Advisory Board or other specialists selected on the basis of expertise and experience. Review is performed on a double-blind basis – the identities of peer reviewers and editors are kept confidential. Peer reviewers must disclose potential conflicts of interests that may affect their ability to provide an unbiased appraisal (see Conflict of Interest Policy below). Peer reviewers complete a referee report form, to provide general comments to the editor and both general and specific comments to the author(s).

Where an author believes that an editor has made an error in declining a paper, they may submit an appeal. The appeal letter should clearly state the reasons why the author(s) considers the decision to be incorrect and provide detailed, specific responses to any comments relating to the rejection of the review. Further advice from members of the journal's Editorial Advisory Panel external experts will be sought regarding eligibility for re-review.

Revision: Most manuscripts require some degree of revision prior to acceptance. Authors should provide two copies of the revised manuscript – one of which should be highlighted to show where changes have been made. Detailed responses to reviewers’ comments, in a covering letter/email, are also required. Review manuscripts may be accepted at this point or may be subject to further peer review. The final decision on acceptability for publication lies with the journal editor.

Post-acceptance
Accepted review manuscripts are edited by the in-house Future Medicine editorial team. Authors will receive proofs of their article for approval and sign off and will be asked to sign a transfer of copyright agreement, except in circumstances where the author is ineligible to do so (e.g. government employees in some countries).

Author disclosure & conflict of interest policy
Authors must state explicitly whether potential conflicts do or do not exist (e.g. personal or financial relationships that could influence their actions) and any such potential conflict of interest (including sources of funding) should be summarized in a separate section of the published review. Authors must disclose whether they have received writing assistance and identify the sources of funding for such assistance. Authors declaring no conflict of interest are required to publish a statement to that effect within the article.

Authors must certify that all affiliations with or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in their manuscript have been disclosed. Please note that examples of financial involvement include: employment, consultancies, honoraria, stock ownership or options, expert testimony; grants or patents received or pending and royalties. This list is not exclusive of other forms of financial involvement. Details of relevant conflicts of interests [or the lack of] must be declared in the ‘Disclosure’ section of the manuscript for all listed authors.

External peer reviewers must disclose any conflicts of interest that could bias their opinions of the manuscript, and they should disqualify themselves from reviewing specific manuscripts if they believe it appropriate. Should any such conflict of interest be declared, the journal editor will judge whether the reviewer’s comments should be recognized or will interpret the reviewer’s comments in the context of any such declaration.

Authorship & contributorship
All authors should meet the ICMJE authorship criteria as follows: (1) they have provided significant input into the design and concept of the study that is the subject of the paper or were pivotal in the acquisition, analysis or interpretation of data; (2) they drafted the paper or were involved in making significant revisions; and (3) they approved the final version of the paper. The corresponding author should accept direct responsibility for the manuscript, including liaising with all authors for their feedback and statements of disclosure, and will be responsible for approval of the final version prior to publication.

Ethical conduct of research
For studies involving data relating to human or animal experimental investigations, appropriate institutional review board approval is required and should be described within the article. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed. For investigations involving human subjects, authors should explain how informed consent was obtained from the participants involved.

Patients’ rights to privacy
Patients have a right to privacy that should not be infringed without informed consent. Identifying information should not be included unless the information is essential for scientific purposes and the patient (or parent or legal guardian) gives written informed consent for publication. Informed consent for this purpose requires that the patient be shown the manuscript to be published. When informed consent has been obtained it should be indicated in the manuscript. In attempting to maintain patient anonymity, identifying details should be omitted where they are not essential. However, patient data should never be amended or falsified. Informed consent should be obtained whenever there is any doubt that anonymity can be assured.

Use of personal communications & unpublished data
Where an individual is identified within a review as a source of information in a personal communication or as a source for unpublished data, authors should include a signed statement of permission from the individual(s) concerned and specify the date of communication.

Clinical trial registration
Future Medicine titles prefer to publish clinical trials that have been included in a clinical trials registry that is accessible to the public at no charge, is electronically searchable, is open to prospective registrants and is managed by a not-for-profit organization, such as www.clinicaltrials.gov (sponsored by the United States National Library of Medicine). Whilst referees will take registration status into account, all well designed and presented trials and corresponding data will be considered for publication.

Errata/corrigenda
Mistakes by either editor or author should be identified wherever possible and an erratum or corrigendum published at the earliest opportunity. We will attempt to contact the author of the original article to confirm any error, and publish an appropriate erratum or corrigendum at the earliest opportunity.

Permissions for reproduced or adapted material
Authors must acknowledge the origin of all text, figures, tables or other information that has been adapted or reproduced from other publications. Authors must provide a copy of the original source documents and should submit permission from the authors of the original work and the original publishers for unlimited use in all markets and media (that includes both electronic and print use in any language).

Duplicate publication/submission & plagiarism
All manuscripts submitted to Future Medicine titles are considered for publication on the understanding that they have not been published previously elsewhere or are under consideration for publication elsewhere. The journal may, however, consider republication of a paper previously published in a language other than English, subject to prominent disclosure of the original source and with any necessary permission. Authors will be asked to certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere, except as described in an attachment, and copies of closely related manuscripts are provided. All submitted articles will be evaluated using plagiarism detection software, which compares the submitted manuscript with full text articles from all major journals databases and the internet. Their unpublished ideas, words or other intellectual property derived from other sources without attribution or permission, and representation of such as those of the author(s) is regarded as scientific misconduct and will be addressed as such.

Misconduct
If misconduct by authors or reviewers is suspected, either pre- or post-publication, action will be taken. An explanation will be sought from the party or parties considered to be involved. If the response is unsatisfactory, then an appropriate authority will be asked to investigate fully. Future Medicine will make all reasonable attempts to obtain a resolution in any such eventuality and correct the record or archive as necessary.
Future Oncology has partnered with Medscape Oncology

Read the most recent articles at:

Medscape Oncology

medscape.com/oncology

Medscape is the leading medical resource most used by healthcare professionals for

Medical News | Original medical news, expert perspectives, and select journal articles in oncology, plus coverage of leading medical conferences

Clinical Reference | Medical reference tools covering diagnosis and treatment information on 15,000 drugs, diseases, procedures, medical devices, and laboratory topics

Continuing Education | Continuing medical education courses across thousands of topics, including breast cancer, lymphoma, and much more

Not a member? Join Medscape for Free at medscape.com/signup
State of the art: hepatocellular carcinoma

Luigi Bolondi*

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, mainly occurring in cirrhotic livers (in 80–90% of cases) after years of chronic inflammation [1,2]. The pathogenesis of HCC is a multistep process associated with changes in the host gene expression of multiple redundant negative-growth regulatory pathways that protect cells against transformation. An imbalance between the proliferation and apoptosis of liver cells is thought to promote tumor development [3]. Annually, 3–6% of cirrhotic patients will develop HCC, mainly men with advanced liver disease. Recent trends in the USA show that men are affected three-times more frequently than women, Asians are affected twice as often as blacks and Hispanics, and blacks are affected twice as often as whites [4]. One explanation for the disproportionate effects of HCC in men may be due to the higher estrogen concentrations present in women, which suppress IL-6 production and inhibit chemically induced liver carcinogenesis [1].

Epidemiology & etiology

HCC is the principal cause of death in patients with compensated cirrhosis worldwide. It is largely a problem of less developed regions, where 83% (50% in China alone) of the estimated 782,000 new cases of liver cell cancer worldwide occur (based on 2012 data) [5]. HCC is the fifth most common cancer in men (554,000 cases; 7.5% of the total) and the ninth in women (228,000 cases; 3.4% of the total) [5]. Regions of high incidence (age adjusted rates per 100,000 inhabitants per year in men) are eastern and south-eastern Asia (31.9 and 22.2, respectively). Intermediate rates occur in southern Europe (9.5) and North America (9.3), and the lowest rates are in northern Europe (4.6) and south-central Asia (3.7) [5].

The global age distribution of HCC cases is related to the dominant viral hepatitis in the underlying population and the age at which it was acquired. For example, the disease burden is highest in areas with endemic hepatitis B virus (HBV) infection, such as in sub-Saharan Africa, where the virus is mainly transmitted at birth (with >90% of these cases becoming chronic HBV carriers). However, the diagnosis of HCC often occurs later in North America and southern Europe, where the most common etiology is HBV or hepatitis C virus (HCV) acquired later in life [2].

Several factors have been reported to increase HCC risk among HBV carriers, including male sex, older age, Asian or African ethnicity, family history of HCC, viral (higher levels of HBV replication, HBV genotype, longer duration of infection or coinfection with HCV, HIV or hepatitis D virus), clinical (cirrhosis) and environmental or lifestyle factors (exposure to aflatoxin, chronic excessive alcohol consumption or tobacco smoking). Other risk factors that increase the risk in HCV-infected patients include coinfection with HIV, HBV, HCV genotype 1b, old age, the presence of diabetes and obesity and a high level of chronic alcohol consumption. However, both HBV and HCV are highly amenable to preventive measures with antivirals or vaccination (for HBV). In Italy, for example, the Italian Liver Cancer (ITA.LI.CA) database reveals a decline in HCV infection with a concomitant increase in alcohol consumption as the primary etiology for HCC [6].

*Department of Medical & Surgical Sciences, Alma Mater Studiorum, University of Bologna, Italy; Digestive Diseases & Internal Medicine, Azienda Ospedaliero-Universitaria di Bologna Policlinico Sant’Orsola-Malpighi, Bologna, Italy; luigi.bolondi@unibo.it

**Keywords**
- diagnosis
- hepatocellular carcinoma
- surveillance
- treatment algorithms
Other factors such as obesity [7] and/or diabetes [8] and the development nonalcoholic fatty liver disease/nonalcoholic steatohepatitis-related cirrhosis may be contributing to the rise in the incidence of HCC in countries where the majority of the population have adopted a western lifestyle (Figure 1).

**Policy for screening & surveillance**

Surveillance (i.e., the process of subjecting high-risk patients to regular ultrasonography [usually every 6 months]) is the best practical approach for improving outcomes. The population for surveillance is already well defined by the European Association for the Study of the Liver (EASL) and America Association for the Study of Liver Disease (AASLD) guidelines (Box 1) [10,11]; however, there are subgroups of patients, particularly those with noncirrhotic nonalcoholic fatty liver disease, for whom the benefits of surveillance remain uncertain. Although there are number of cohort studies suggesting the benefits of surveillance in defined populations in the early diagnosis of HCC [12], there are in fact no randomized controlled studies, as patients would not grant informed consent to not being surveyed [13].

Macroregenerative nodules with or without liver cell dysplasia are common causes of false-positive results with ultrasound without contrast agents and patients with these may progress to HCC (up to 10% per year) or may even disappear during follow-up [14].

**Diagnosis & staging**

In HCC, tumor characteristics, functional status and liver function are better predictors of disease severity and patient survival than tumor-related criteria alone (i.e., tumor, node and metastases classification). There is, however, no universally agreed staging system for HCC. In Europe, either the Barcelona Clinic Liver Cancer (BCLC) [15] or the Cancer of the Liver Italian Program (CLIP) [16] scoring systems are currently used.

Triphasic spiral (multidetector) computed tomography (CT) and dynamic contrast-enhanced MRI should be considered to be the standard techniques for intrahepatic tumor staging when a treatment decision has to be taken. The sensitivity of these techniques for

---

**Figure 1.** Trends associated with the incidence of hepatocellular carcinoma worldwide.

†Data taken from [9].
the detection of the ‘typical’ pattern of HCC vascularity (hypervascularization in the arterial phase and wash-out in the portal–venous phases) has been evaluated in a number of studies [17–20]. However, a more recent study has shown that imaging techniques (CT and MRI) have a low sensitivity (∼50–60%) for the diagnosis of early-stage HCC [21]. Current EASL and AASLD guidelines recommend CT and MRI (and not contrast-enhanced ultrasound) for the noninvasive diagnosis of HCC (lesions >1 cm) in patients with cirrhosis or those with HBV infection without fully developed cirrhosis. The value of contrast-enhanced ultrasound in recognizing the typical vascular pattern of HCC is, however, acknowledged by the guidelines from both the Italian Association for the Study of the Liver (AISF) [22] and the World Federation for Ultrasound in Medicine and Biology (WFUMB) and Ultraschall in der Medizin/European Journal of Ultrasound [23], as well as from Asia [24,25] and other national bodies, such as NICE [26].

Improvements in imaging techniques provide new diagnostic options, essentially based on new contrast agents for MRI and their ability to characterize a different aspect of the neoplastic tissue based on the cellular and not on the vascular pattern. This is an innovative concept and represents an interesting perspective for improving the noninvasive diagnosis of liver nodules, particularly in early HCC without the typical pattern of vascularity and in true hypovascular HCC. The introduction of MRI with hepatobiliary contrast agents has opened the way to a new scenario in practice guidelines; in particular, this imaging technique is already included in Japanese guidelines not as an initial diagnostic approach, but for the early identification of nodules without a typical vascular pattern and in cases where liver biopsy is not feasible. Recently published studies have confirmed the value of the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) MRI in the diagnosis of small hypovascular HCC nodules in cirrhotic patients under surveillance [27,28]. A consensus report of radiologists concluded that hepatocyte-specific contrast agent (Gd-EOB-DTPA), with its unique pharmacokinetic features, should be considered for future diagnostic algorithms for the evaluation of liver nodules [29].

**Evolution & challenges of treatment**

An important step in the management of early HCC is the application of an appropriate and accurate staging system – ideally, one that stratifies patients for treatment and predicts prognosis. The BCLC standard classification has been validated in different studies and is endorsed by the AASLD and the EASL. Although the BCLC system links tumor stage with the treatment strategy, some recent studies have demonstrated that in early and very early disease, a significant proportion of patients do not receive
curative treatments or receive treatments that are not recommended by practice guidelines. This gap between the theoretically ideal behavior and real-life treatment approaches in early HCC is related to the individual characteristics of each patient, as well as local expertise and resources [30]. Therefore, the decision to treat HCC is often made on an individual basis, taking into account the size and location of the lesion, coagulation parameters and patients’ willingness for treatment.

Similarly, patients with intermediate-stage HCC also represent a cohort with varying tumor burdens, liver functions (Child–Pugh class A or B), disease etiologies and general health statuses [31]. The implication of this heterogeneity is that not all patients will benefit from transarterial chemoembolization (TACE) to the same degree [31–33]; some patients may benefit more from other treatment options [33], and prognostic factors for a response to TACE could improve treatment decisions and thus patient outcomes. A subclassification of intermediate-stage HCC into four different groups as well as the quasi-BCLC stage C group has recently been published (Figure 2) [34]. Consistent with the Japan Society of Hepatology (JSH) guidelines [24], alternatives to TACE are proposed for the management of intermediate-stage HCC, because in the real world, TACE is only appropriate in approximately two-thirds of these patients [30]. Therefore, this new subclassification system allows physicians to adopt a more rational treatment approach depending on the disease and patients’ characteristics.

Managing patients with HCC should be under the care of a multidisciplinary team that typically includes hepatologists, surgeons, radiologists, oncologists and pathologists. Therapy for HCC may include resection, locoregional therapy, systemic therapy, transplantation or a combination of these modalities. The best studied nonsurgical interventions are radiofrequency ablation, bland embolization/TACE and yttrium-90 selective internal radiation therapy (or radioembolization). The only available systemic therapy is based on sorafenib, a multi-kinase inhibitor that, in a randomized, placebo-controlled, double-blind study of 602 patients, demonstrated a survival advantage of 2.7 months...
(p < 0.001) over the placebo group [36]. Similar results were found in an Asian trial of sorafenib versus placebo [37]. However, once again, a study in the real-world clinical setting showed that sorafenib is in fact used across all stages of HCC (mainly in patients with Child–Pugh class A liver function) [38].

Future perspective
There are now a number of pathways that have been identified for molecularly targeted approaches to HCC treatment [39], but unfortunately, many new targeted treatments (including sunitinib, linifanib, brivanib and the combination of sorafenib plus erlotinib) have failed to show an improvement in overall survival compared with sorafenib as a single agent in the first-line setting, or compared with placebo in the second-line setting in the case of brivanib [40]. Trials are ongoing with tivantinib (in mesenchymal–epithelial transition factor [met]–high tumors) [41], refametinib (in ras-high tumors) [42] and regorafenib (in met-low tumors) [43]. These treatments as well as locoregional approaches may represent the future of HCC care (Box 2).

Financial & competing interests disclosure
Over the last 2 years, L Bolondi has received lecture and consulting fees as well funding for clinical trials from Sirtex Medical and Bayer Healthcare, Bristol-Myers Squibb, Abbott, Novartis and Daiichi Sankyo. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References
6 Santi V, Buccione D, Di Micoli A et al. The changing scenario of hepatocellular carcinoma over the last two decades in Italy. J. Hepatol. 56(2), 397–405 (2012).
16 Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP)


NICE. Sonovue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. www.nice.org.uk/guidance/dg3


Piscaglia F, Bolondi L. The intermediate hepatocellular carcinoma stage: should treatment be expanded? Dig. Liver Dis. 42(Suppl. 3), S258–S263 (2010).


Evidence-based integration of selective internal radiation therapy into hepatocellular carcinoma management

Bruno Sangro*

The unique double irrigation of the liver (through the portal vein and the hepatic artery) and the predominantly arterial irrigation of liver tumors, particularly primary liver cancer, are the basis for the intra-arterial therapy of hepatocellular carcinoma (HCC). The most commonly used techniques are transarterial chemoembolization (TACE) with or without drug-eluting beads (DEBs) and transarterial radioembolization, which is also called selective internal radiation therapy (SIRT). TACE combines local drug delivery with concurrent tumor-feeding artery embolization. SIRT is a form of brachytherapy in which intra-arterially injected microspheres loaded with yttrium-90 serve as sealed sources for internal radiation purposes.

Keywords
- brachytherapy
- hepatocellular carcinoma
- selective internal radiation therapy

Transarterial chemoembolization

The evidence that supports the use of TACE for the palliative treatment of unresectable HCC comes from two randomized controlled trials in selected patients with preserved liver function [1,2] and three meta-analyses [3–5]. TACE has thus been established as the standard of care for patients in the intermediate stage of the Barcelona Clinic Liver Cancer (BCLC) staging system (i.e., those with multinodular HCC, relatively preserved liver function, an absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread) [6,7]. However, it should be noted that approximately half of the patients recruited in the two positive trials had one or two tumor nodules (i.e., early-stage HCC for which ablation was deemed unfeasible) [1,2]. The concept of DEB-TACE is to inject intra-arterially embolizing particles that have been loaded in vitro with cytotoxic agents and slowly release them into the tumor environment [8,9]. Although randomized trials have not shown the superiority of DEB-TACE versus conventional TACE in terms of tumor response or overall survival, DEB-TACE has provided a more standardized way of performing TACE [10]. A recent consensus from a panel of experts has recommended a series of absolute and relative contraindications for the treatment of patients in the intermediate stage, which includes large, single tumors (Table 1) [11]. On the other hand, SHARP was the pivotal Phase III randomized controlled trial that proved that the systemic agent, sorafenib, prolonged the survival of HCC patients [12]. The target population consisted of patients who were not amenable for TACE, including those in the advanced stage (i.e., patients with poor performance status, vascular invasion or extrahepatic metastases) and those in the intermediate stage that had progressed or were considered poor TACE candidates [12].

Selective internal radiation therapy

SIRT has a clear palliative role in the management of HCC by inducing tumor necrosis and delaying progression [13–16]. Tumor shrinkage occurs almost invariably after SIRT, although it
Table 1. Suggested contraindication to transarterial chemoembolization in intermediate-stage hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompensated cirrhosis (Child–Pugh class B ≥8)</td>
<td>Comorbidities involving compromised organ function: active cardiovascular or lung disease</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Untreated varices at high risk of bleeding</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Bile duct occlusion or incompetent papilla due to stent or surgery</td>
</tr>
<tr>
<td>Refractory ascites</td>
<td></td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td></td>
</tr>
<tr>
<td>Extensive tumor with massive replacement of both entire lobes</td>
<td></td>
</tr>
<tr>
<td>Severely reduced portal vein flow</td>
<td>Tumor size ≥10 cm</td>
</tr>
<tr>
<td>Technical contraindications to hepatic intra-arterial treatment (e.g., untreated arteriovenous fistulae)</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency (creatinine ≥2 mg/dl or creatinine clearance &lt;30 ml/min)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from [11].

may take 3–6 months for the optimal response to manifest, and median time to response can consequently be as long as 6 months. The available data suggest that the ability of SIRT to achieve complete pathological necrosis is similar, if not better than, conventional TACE [17]. The lack of a significant ischemic effect enables the consideration of SIRT for patients with macrovascular invasion and thrombosis [18–20].

For patients in the intermediate stage, cohort series and comparative effectiveness studies [21–23] (including a small pilot randomized controlled trial [24]) suggest that there is no survival difference between SIRT and TACE [25]. Hence, many centers have recognized SIRT as a

---

**Figure 1.** Across-study evaluation of the median overall survival with selective internal radiation therapy (either with glass or resin microspheres) across the spectrum of patients with early- to advanced stage hepatocellular carcinoma [14–16].
Evidence-based integration of SIRT into hepatocellular carcinoma management

**Table 2. Suggested indications for selective internal radiation therapy in hepatocellular carcinoma (based on retrospective and prospective cohort studies and case-control studies).**

<table>
<thead>
<tr>
<th>HCC stage</th>
<th>SIRT indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate HCC</td>
<td>Single, two to three nodules, Child–Pugh class A, normal liver function, multifocal (bilobar or tumor burden 20–40%), only if bilirubin &lt;2 mg/dl</td>
</tr>
<tr>
<td>Advanced HCC</td>
<td>Branch or main portal vein invasion, no extrahepatic disease, normal liver function</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; SIRT: Selective internal radiation therapy.
Adapted from [26].

While the European Society of Medical Oncology and the National Comprehensive Cancer Network have listed SIRT as a treatment option for HCC [30,31], the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver do not recommend its use outside of clinical trials [6,7]. Randomized studies would probably be required in order to determine whether SIRT would be universally accepted as a first-line option in a defined subgroup of patients with HCC. Several international randomized controlled trials are now in progress in order to investigate the role of SIRT when added to sorafenib (NCT01126645 and NCT01556490) or in head-to-head comparisons of sorafenib versus SIRT in terms of prolonging the survival of intermediate- to advanced-stage HCC patients (NCT01887717, NCT01135056 and NCT01482442). Furthermore, a randomized Phase II trial is comparing DEB-TACE and SIRT in intermediate-stage disease with time to progression as the primary end point (NCT01381211).

**Figure 2.** Median overall survival reported across studies with sorafenib and selective internal radiation therapy among patients with portal vein thrombosis.

1 Data taken from [27].
2 Data taken from [28].
3 Data taken from [13].
4 Data taken from [15].
† Data taken from [19].
‡ Data taken from [16].
†† Data taken from [19].
‡‡ Data taken from [16].

Figure 2. Median overall survival reported across studies with sorafenib and selective internal radiation therapy among patients with portal vein thrombosis.
Novel applications of SIRT that deserve further research include: the application of high radiation doses to small sectors of liver tissue in ‘radiation segmentectomy’; right-lobar SIRT in order to induce significant contralateral hypertrophy, which may enable anatomic liver resections that would be otherwise contraindicated because of a small future liver remnant; and the application of SIRT for enabling downsizing to liver transplantation or percutaneous ablation [26].

References


25. Moreno-Luna LE, Yang JD, Sanchez W, et al. Efficacy and safety of transarterial...


CNS Oncology

Don’t be left behind. Keep up with the latest topics in CNS oncology

SUBSCRIBE NOW
Receive a 10% discount on your subscription when you quote the code CNS14.

CNS Oncology addresses key issues in the diagnosis, staging and treatment of disease by exploring the best patient-centered clinical research and presenting this information both directly, as clinical findings, and in practice-oriented formats of direct relevance to the clinic.

“It is great to learn that CNS Oncology has been accepted for indexing by MEDLINE. [The journal] … will therefore be a leading platform for authors looking to publish their work. The future is certainly promising for CNS Oncology.”
Alba Brandes, Senior Editor, CNS Oncology

www.futuremedicine.com
Clinical studies in hepatocellular carcinoma

Valérie Vilgrain*, Mohamed Abdel-Rehim, Annie Sibert & Maxime Ronot

According to clinicaltrials.gov (a clinical trials registration site), there are currently 31 trials that are evaluating selective internal radiation therapy (SIRT) in hepatocellular carcinoma (HCC; consisting of nine completed studies, 20 ongoing studies and two studies of unknown status). These studies reflect the considerable interest in the potential application of this procedure in not only advanced HCC, but also in intermediate HCC (with studies evaluating SIRT vs transarterial chemoembolization [TACE]), early HCC as a bridge to transplantation (based on retrospective studies and a new trial from a French institution that will evaluate SIRT vs TACE) and in the neoadjuvant treatment setting (presurgery).

To date, the best published evidence for SIRT comes from retrospective and prospective cohort studies and case–control studies in advanced HCC [1–4]. One of the largest retrospective clinical case series evaluated 325 patients (from 2003 to 2009) with multinodular disease (75.9%) who had been treated with SIRT at eight European centers. The median duration of survival was 12.8 months (95% CI: 10.9–15.7) with elevated bilirubin reported as the main grade 3 adverse event in 5.8% of patients [2]. As discussed by Sangro in this supplement, SIRT (using either resin or glass microspheres) is effective across the spectrum of patients with early- to advanced-stage HCC [3,5,6], including patients with main and branch portal vein thrombosis (PVT), who generally have a poor prognosis (Figure 1) [2,7]. As a consequence, a number of prospective Phase III studies are evaluating SIRT in advanced HCC (stratifying patients with or without PVT). Some of these studies are combining SIRT plus sorafenib, while others are comparing SIRT versus sorafenib (Table 1).

Combining SIRT with Y-90 resin microspheres plus sorafenib

**SORAMIC**

Sorafenib in combination with local microtherapy guided by gadolinium-EOB-DTPA-enhanced MRI in patients with inoperable HCC (SORAMIC; EudraCT no.: 2009-012576-27; NCT01126645) is a European, multicenter, independent academic trial. Sponsored by the University of Magdeburg (Germany), between 30 and 40 centers in 12 countries (Germany, France, Belgium, The Netherlands, Switzerland, Austria, Italy, Poland, Slovenia, Spain, Turkey and recently the UK) are involved in the trial. SORAMIC is composed of an imaging substudy and two treatment substudies in patients allocated to either ablation with curative intent or palliative treatment (Figure 2). The palliative treatment study aims to evaluate the safety and efficacy of Y-90 resin microspheres (SIR-Spheres®, Sirtex Medical Ltd, Australia) plus sorafenib versus sorafenib alone in nonresectable HCC in 375 patients. Patients who are eligible for the trial include those with modified Barcelona Clinic Liver Cancer (BCLC) stage B and C disease (distant metastases except for the lung) who are not eligible for TACE (large tumors and diffuse disease), with Child–Pugh class A and B (up to 7 points) and bilirubin elevated.

*Author for correspondence: Tel.: +33 140 875 358; Fax: +33 140 870 548; valerie.vilgrain@bjn.aphp.fr

KEYWORDS

- HCC • hepatocellular carcinoma • portal vein thrombosis • prospective
- PVT • randomized clinical trials • selective internal radiation therapy • SIRT
Figure 1. Selective internal radiation therapy for hepatocellular carcinoma with or without portal vein thrombosis. Data taken from [7,8].

Table 1. Ongoing prospective randomized clinical trials of selective internal radiation therapy (with Y-90 resin and glass microspheres) in hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Parameter (n)</th>
<th>SIRveNIB†</th>
<th>YES-P‡</th>
<th>SARAH†</th>
<th>SORAMIC‡</th>
<th>STOP‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>360</td>
<td>328</td>
<td>440</td>
<td>665</td>
<td>400</td>
</tr>
<tr>
<td>Control arm</td>
<td>Sorafenib</td>
<td>Sorafenib</td>
<td>Sorafenib</td>
<td>Sorafenib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Experimental arm</td>
<td>SIRT</td>
<td>SIRT</td>
<td>SIRT</td>
<td>SIRT + sorafenib</td>
<td>SIRT + sorafenib</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Overall survival</td>
<td>Overall survival</td>
<td>Overall survival</td>
<td>Overall survival</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Region</td>
<td>Asia–Pacific</td>
<td>USA and Italy</td>
<td>France</td>
<td>EU</td>
<td>Global</td>
</tr>
<tr>
<td>Clinicaltrials.gov identifier</td>
<td>NCT01135056</td>
<td>NCT01887717</td>
<td>NCT001482442</td>
<td>NCT01126645</td>
<td>NCT01556490</td>
</tr>
</tbody>
</table>

†With Y-90 resin microspheres. ‡With Y-90 glass microspheres. SIRT: Selective internal radiation therapy.

<30 μmol/L. Patients with the following criteria are excluded: an Eastern Cooperative Oncology Group (ECOG) performance status >2; life expectancy <16 weeks; known glomerular filtration rate <30 ml/min/1.73 m²; and whole-liver tumor burden >70%. Patients will be stratified by the presence of PVT and clinical study center. The primary end point is overall survival. Secondary end points include: health-related quality of life (HRQoL), safety and overall survival with and without PVT. The trial started in December 2010, with study completion expected by Q2 2017.

**Sorafenib versus SIRT with Y-90 resin microspheres**

In the Phase III SHARP and Asia–Pacific studies, sorafenib was associated with high rates of grade ≥3 adverse events, including hand–foot syndrome (8–10%) and diarrhea (6–8%), as well as fatigue (3–4%) and weight loss (2%) [9,10]. Consequently, a number of head-to-head studies are now ongoing in order to evaluate the relative efficacy and safety of sorafenib versus SIRT.

- **SIRveNIB**

SIRveNIB (NCT01135056) is an ongoing, open-label, randomized controlled Phase III trial that is being conducted at 28 Asia–Pacific sites. The study aims to recruit 360 patients with locally advanced HCC with or without branch PVT or incomplete main PVT that is not amenable to resection or transplantation or cannot be optimally treated with local ablative techniques. Eligible patients are randomized (1:1) to either sorafenib or SIRT with Y-90 resin microspheres and are stratified by center and the presence of PVT. The primary end point is overall survival.
Secondary end points include: progression-free survival, time to progression, response rate, safety and HRQoL. The study commenced in July 2010 and is expected to be completed in 2017.

**SARAH**

SARAH (NCT01482442) is a prospective, randomized, open-label trial that is being conducted at 23 sites in France. Like SIRveNIB, the study is evaluating the safety and efficacy of SIR-Spheres (Y-90 resin microspheres) versus sorafenib, but unlike SIRveNIB, SARAH includes patients with complete PVT. In addition, SARAH is recruiting patients who have had no objective responses after two TACE procedures at most. Patients are being stratified by ECOG performance status, vascular invasion, prior TACE and study site. The primary end point is overall survival. Secondary end points include time to progression, safety and HRQoL, as well as healthcare costs. The study, which commenced in December 2011, aims to recruit 440 patients and is expected to be completed in 2016.

At the completion of these studies, a meta-analysis of the data from SIRveNIB and SARAH is planned, during which minor differences in the study designs will be taken into account (e.g., SIRveNIB allows a maximum of one SIRT procedure vs SARAH, which allows for a maximum two SIRT procedures in each lobe).

**Conclusion**

In conclusion, there are a number of important trials ongoing with SIRT in advanced HCC that are recruiting a large number of patients. Each trial aims to address different questions, which will likely impact on the future management of advanced HCC.

**Financial & competing interests disclosure**

V Vilgrain has received honoraria for congress presentations as well as a research grant from Sirtex for the SARAH study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

**References**


SYMPOSIUM PAPER Vilgrain, Abdel-Rehim, Sibert & Ronot


The effectiveness of selective internal radiation therapy in challenging cases of liver-predominant unresectable hepatocellular carcinoma

Peter Malfertheiner\textsuperscript{\ast}, Chris Verslype\textsuperscript{2}, Frank T Kolligs\textsuperscript{3}, Kerstin Schütte\textsuperscript{1}, V Vandecaveye\textsuperscript{3}, Philipp M Paprottka\textsuperscript{1} & Jens Ricke\textsuperscript{4}

Local and locoregional therapies are well established in the management of various stages of hepatocellular carcinoma (HCC). In very-early-stage and early-stage HCC (Barcelona Clinic Liver Cancer stage O/A), radiofrequency ablation is the best option for patients with a limited number of small lesions (≤3 cm), which are either not amenable to resection or as an alternative to surgery in patients with liver cirrhosis. Radiofrequency ablation can successfully be combined with transarterial chemoembolization (TACE) in tumors with a diameter of between 3 and 5 cm with the intention to reduce local relapses [1]. For intermediate-stage HCC (Barcelona Clinic Liver Cancer stage B), TACE has become the standard of care and is recommended by international guidelines [2]. More recently, selective internal radiation therapy (SIRT; or radioembolization using yttrium-90 microspheres) has been indicated as a treatment option in consensus recommendations in the USA and Europe [3,4].

While TACE improves survival for intermediate-stage HCC (as a whole), not all patients derive the same benefit from TACE [5]. For the heterogeneous population of patients with intermediate-stage HCC, who are characterized by widely varying tumor burdens, morphologies (i.e., ‘focal/nodular’, ‘massive’ and/or ‘diffuse/infiltrating’) [6,7] and liver functions (Child–Pugh class A or B [8]), some patients may benefit from treatments other than TACE [9,10,11]. In a recent paper from a multidisciplinary group of European experts in the treatment of HCC with locoregional therapy, guidance on the application of TACE in HCC (indications and contraindications) was provided based on the latest clinical experience (Tables 1 & 2). This paper discusses the relative role of TACE and SIRT in the management of unresectable HCC in cases where the guidance on the optimal treatment remains equivocal.

HCC with a large tumor volume with or without portal vein invasion

TACE is contraindicated in patients with a large tumor burden (characterized by multinodular (>5 nodules) and/or large tumors in the liver) [9,10]. Portal vein thrombosis, especially if ipsilateral, is also a contraindication for TACE, whereas SIRT may still be safely administered in these patients with a favorable median survival [12–14]. Moreover, early published safety reports indicate that sorafenib (400 mg twice daily) administered at 14 days post-SIRT is well tolerated [15,16], although the published clinical experience with SIRT and sorafenib is still limited at this time.

In order to test whether the combination of SIRT with Y-90 resin microspheres followed by sorafenib offers any advantage over sorafenib alone with respect to survival in the palliative setting, the Phase III SORAMIC study was initiated. SORAMIC is a multicenter, randomized controlled trial currently with >200 patients recruited into the palliative arm [EudraCT no.: 2009-012576-27; NCT01126645] [16]. The clinical presentation and outcomes of two patients...
from this study with large tumor volumes are outlined below.

- **Case history 1**
  **Presentation**
  A 77-year-old male presented with a mass detected incidentally on ultrasound in January 2011. He had no history of chronic liver disease and was asymptomatic (Eastern Cooperative Oncology Group [ECOG] performance status 0). The patient was obese (BMI = 31.2 kg/m²) with a 23-year history of Type 2 diabetes mellitus. His alcohol consumption was described as moderate (three bottles of beer per day). Liver cirrhosis (nonalcoholic steatohepatitis) was confirmed clinically and on ultrasound. Further investigation revealed that he had good liver function (Child–Pugh class A). No significant pathological findings were observed with esophagogastroduodenoscopy or colonoscopy. Liver biopsy confirmed the presence of well-differentiated (G1) HCC. Contrast-enhanced MRI showed a large HCC lesion (9.7 × 14.5 cm) in the central-right liver lobe (segments IV, V and VIII; **Figure 1A**). The portal vein was patent and there was no evidence of extrahepatic disease.

**Treatment & outcomes**

The patient was not considered to be a suitable candidate for surgery due to the tumor size, its central location and the presence of liver cirrhosis, or TACE due to the tumor size, and so he consented to participate in the SORAMIC study. He received sequential lobar treatment with SIRT (right lobe [March 2011] then left lobe [April 2011]) followed by sorafenib for 17 months until September 2012. Upon disease progression, SIRT was repeated (using a selective right lobar treatment approach). Sorafenib was continued until 12 December 2012 when systemic therapy was stopped as the response to treatment was slow. The patient died in May 2013 (26 months after the first SIRT procedure).

We concluded that this patient with a large tumor achieved a long survival after SIRT without significant deterioration in liver function or performance status, even after repeat SIRT and sorafenib treatment.

- **Case history 2**
  **Presentation**
  A 67-year-old male with a history of metabolic syndrome (arterial hypertension, hypercholesterolemia...
and Type 2 diabetes mellitus requiring insulin) presented with jaundice and rapid and unexpected weight loss (10 kg within the previous 5 weeks). The patient had a good performance status (ECOG 0). Sonography revealed fatty infiltration of the liver and cirrhosis. The patient had markedly elevated α-fetoprotein serum levels of 68.96 μg/ml and hyperbilirubinemia (total bilirubin: 54.8 μmol/l [3.2 mg/dl]) and accompanying liver dysfunction (prothrombin time-international normalized ratio [INR]: 0.97; albumin: 39.1 μmol/l [26.97 g/dl]). Esophageal varices and mild esophageal reflux disease (Los Angeles grade A) were identified on esophagogastroduodenoscopy and diverticulosis with portal colonopathy was identified on colonoscopy. Contrast-enhanced MRI showed multifocal HCC lesions of the right and left liver lobes with infiltration of the right branch of the portal vein on portal venous-phase images. As shown in Figure 2A, part of the tumor was hyperperfused and part of the tumor was hypoperfused. The largest tumor in the liver was >5 cm. HCC was confirmed by biopsy.

Further analysis revealed that the jaundice was due to extrahepatic obstruction of the bile duct (due to hilar lymph node involvement), which was relieved by stenting before treatment of the HCC nodules in the liver.

**Treatment & outcomes**

The patient consented to participate in the SORAMIC study and received right lobar SIRT (December 2011) followed by sorafenib (800 mg/day), which was well tolerated. Imaging at 18 months post-SIRT (Figure 2B) showed a complete response with scarring and some residual disease with both contralateral hypertrophy and ipsilateral shrinking without evidence of further progression beyond the liver. We concluded that a complete response to SIRT is still possible even in patients with locally advanced, multinodular HCC and portal vein invasion who are outside the normal guideline criteria and therefore difficult to treat according to current algorithms.

### Discussion

Both TACE & SIRT are treatment options in patients with hypervascular intermediate-stage tumor(s)

While the current guidelines recommend TACE in intermediate-stage HCC [2], there is some evidence that TACE is less effective for larger tumors (≥4 cm) [5]. Evidence from surgical case series has shown that, compared with patients with smaller lesions (≤5 cm), patients with larger lesions were also much more likely to present portal vein invasion (20.8 vs 4.9%; p < 0.01) [17]. In such cases, TACE would be contraindicated (Table 1) [9].

The decision to treat with SIRT in large-volume HCC is independent of the portal vein involvement, but needs to be carefully considered in the context of liver function

Memon et al., in a study of 291 HCC patients treated with SIRT, found that very good survival can be achieved with portal vein occlusion (PVO) and Child–Pugh class A, but not with Child–Pugh class B of >7 points [13].

**Follow-up post-SIRT & sorafenib**

It is notable that even in patients with large lesions, SIRT followed by sorafenib therapy
was well tolerated and repeat treatment with SIRT was possible. Similarly, the response to right lobar SIRT followed by sorafenib in case 2 was excellent, despite the presence of multifocal HCC lesions of the right and left liver lobes with infiltration of the right branch. With a complete response to SIRT plus sorafenib recorded at 18 months, this patient could have been a candidate for surgery. However, a non-ST-segment elevation myocardial infarction was recorded in September 2013 and an ischemic ulcer on the left calf was recorded in August 2013. Sorafenib was stopped in August. At last contact (December 2013), the patient was doing well.

Infiltrative HCC

While compromised portal vein blood flow is usually considered a contraindication for TACE [18] due to the increased risk of complications such as liver abscess or decompensation of cirrhosis [19], the lack of significant macroembolic effects on SIRT means that portal vein thrombosis is not an absolute contraindication [12]. Patients with infiltrative HCC, particularly solitary tumors invading a segmental or lobar branch of the portal vein, may be considered as potential candidates for SIRT [20].

● Case history 3

Presentation & clinical history

A 58-year old male with a history of familial hypercholesterolemia and abnormal liver tests for more than 20 years presented with pain in the right subcostal area. There were no clinical signs of liver disease. Analysis of the biochemistry showed that the bilirubin level was at 1.7 mg/dl, INR was at 1.3, platelets were at $75 \times 10^9/l$ and $\alpha$-fetoprotein, hemoglobin and serum creatinine were normal. Liver function was determined to be Child–Pugh class A. Ultrasound revealed a hypointense nodule in segment 8 of the liver (1 cm) together with splenomegaly and collaterals in the abdominal wall. An MRI showed heterogeneous arterial blushing of segments 4 and 8,
with absence of visualization of the peripheral branches of the portal veins in these segments. This zone was hyperintense on diffusion-weighted imaging (b600 sequences) and was surrounded by b600 hyperintense nodules (Figure 3A). On esophagogastroduodenoscopy, there was hypertensive gastropathy; a CT scan of the thorax showed no metastases. Laparoscopically taken liver biopsies confirmed an infiltrative HCC on the background of a nonalcoholic fatty liver disease cirrhosis.

Treatment work-up & outcomes
The pre-SIRT work-up determined that there was no need for embolization of the gastroduodenal artery due to the presence of significant ostial stenosis of the coeliac trunk, leading to retrograde flow in the gastroduodenal artery. Lung shunting was 7.5% with no leakage to the stomach or abdominal wall. A full-liver SIRT procedure was subsequently performed using yttrium-90 resin microspheres. Six months later, MRI (Figure 3B) showed a disappearance of the previous arterial hypercaptation of segments 4/8, together with the loss of the b600 hyperintense signals. There were edematous aspects of segments 1, 6 and 7 and the anterior parts of segments 2/3. Laparoscopically taken biopsies showed an inflammatory ductular reaction and no evidence of residual HCC, and the patient was considered as having a complete response. Following this efficient downstaging, the patient underwent cadaveric liver transplantation 1 year later. The explant liver confirmed the absence of HCC.

In conclusion, this case study illustrates the potential effectiveness of SIRT for the downstaging of patients with limited (early-stage) infiltrative HCC.

Discussion
Even though infiltrative HCC accounts for up to 13% of HCC cases, its diagnosis, staging & treatment remains poorly characterized in the literature. HCC, typically occurring on a background of chronic liver disease, can have various morphological appearances (i.e., focal/nodular or infiltrating). The infiltrative subtype (accounting for up to 13% of all HCC cases [21]) is one of the most difficult of these to recognize on early surveillance imaging [22], often blending into the background of the cirrhotic liver. However,
Figure 3. Case 3: MRIs. (A) MRI, baseline. (i) Arterial phase: arterial blush of segments 4 and 8 (arrows) (ii) Portal-venous phase: no wash-out; diminished visualization of small portal branches, suggestive of tumoral infiltration (arrows); (iii) Diffusion-weighted imaging (b600 sequences): moderate hyperintensity in segment 4 and 8 (arrows). (B) 6 months post-treatment MRI. (i) Arterial phase: no arterial blush in segment 4/8 anymore; arterial hypercaptation in segment 1, 7, 6 with geographic distribution; (ii) Venous phase: no visible lesions; (iii) Diffusion-weighted imaging (b600): no hyperintense signal.
certain imaging characteristics can provide vital clues as to the presence of infiltrative HCC, including differing signal intensities on the T1 and T2 sequences of MRI and the presence/appearance of portal vein thrombus. When portal vein invasion is extensive, the tumor can fill the peripheral portal vein branches, commonly displaying significant arterialization of the tumor thrombus.

In part due to its late diagnosis in most patients, the prognosis of patients with infiltrating HCC is considerably worse compared with patients who have a focal/nodular subtype [23–26]. Even in patients with small tumors (≤2 cm), disease-free survival in patients with HCC accompanied by microinvasion is significantly worse than for those without microinvasion in the surgical setting following wide-margin resection [27]. In addition, the presence of portal hypertension also increases the likelihood of complications to surgery. The poor demarcation and difficulty of defining the extent of infiltrating HCC on cross-sectional imaging impedes: appropriate patient selection; the ability to adequately target the lesion; and the determination of the subsequent response to locoregional treatment. Moreover, the limited evidence with conventional TACE suggests that the treatment of infiltrating HCC can be associated with significant morbidity and mortality and yield poor long-term outcomes [28].

If the current clinical guidelines were followed strictly, systemic treatment with sorafenib would have been recommended for this patient upon initial presentation

Based on current guidelines [2], sorafenib is the mainstay for the treatment of advanced HCC (i.e., in patients with portal vein invasion and at least partially preserved liver function). However, the published experience with sorafenib for the management of invasive HCC is limited to a few patients in large studies. As shown in Figure 4, however, patients in the advanced stages of HCC treated by SIRT (based on respective analyses) have very similar median overall survivals (in the range of 6–10 months) [29,30] to those reported in the Phase III clinical trials with sorafenib (6.5–10.7 months) [31,32]. For patients with segmental or branch portal vein invasion, a median overall survival with SIRT of 10.8 months (95% CI: 8.3–11.4 months) [33,34] also compare favorably with those previously reported with drug-eluting beads-TACE of 8.8–11.4 months [33,34] and with conventional TACE of 7.0–8.3 months [35,36].
The evidence so far indicates that, particularly for branch PVO, SIRT should not be assumed to have an increased risk of liver-related adverse events or worsened survival compared with patients without PVO in the advanced-stage disease setting. However, further prospective comparisons of the relative safety and efficacy of systemic (with sorafenib) versus locoregional treatment (e.g., SIRT) in advanced, localized HCC are clearly needed.

Downstaging for liver transplantation
Early evidence from a retrospective cohort study of patients who were downstaged for transplantation using locoregional treatment has been promising [37]. Only two out of 14 patients developed tumor recurrence after a median follow-up period of 35 months (range: 1.5–50 months) after liver transplantation [37]. Notably, however, in this mainly TACE-treated cohort, it was the presence of noninfiltrative HCC that was the

Figure 5. Case 5: contrast-enhanced computed tomography. (A) Baseline, pretreatment imaging showing a hepatocellular carcinoma in the right liver lobe prior to the first transarterial chemoembolization and (B) imaging showing a progression after six sessions of transarterial chemoembolization.
sole predictor of successful downstaging and improved outcome on multivariate analyses.

**Conclusion**
In conclusion, the multimodal treatment of patients with advanced HCC (with locoregional treatment and surgery) is a new and promising field of investigation. Unlike TACE, SIRT appears to be able to induce a complete response even in advanced, infiltrative HCC with vascular invasion, opening up the possibility for downstaging to resection or transplantation; however, the evaluation of the response using imaging alone remains a challenge. Further prospective evaluation of the safety and efficacy of SIRT in this setting is clearly needed.

**Treatment of HCC with SIRT after failed TACE**
Although the current evidence for SIRT after TACE in HCC is limited [30,38], SIRT appears to be well tolerated post-TACE as in treatment-naive patients.

**Case history 4**
Presentation & clinical history
A 75-year-old male with liver cirrhosis (Child–Pugh class A) due to chronic hepatitis C presented with a single large HCC nodule (12 × 8 cm) of the left lobe, which showed hypervascularization and wash-out on contrast-enhanced ultrasound and computed tomography; α-fetoprotein levels were at 6.8 ng/ml. The patient had comorbid Type 2 diabetes mellitus, arterial hypertension (treated with three antihypertensive medications) and had undergone previous surgery, including a Billroth-II gastrectomy.

HCC staging
The patient had a single hypervascularized HCC nodule. An extended left-sided hemihepatectomy was technically feasible, but was considered to be a high-risk approach. The decision was taken to perform one session of superselective TACE and restage at 8 weeks after the procedure. If there was no tumor progression, the patient would be re-evaluated for surgery.

Treatment & outcomes
TACE was poorly tolerated and associated with abdominal pain, fever and increased liver enzymes and bilirubin, resulting in readmission to hospital. Eight weeks after TACE, the tumor was still highly hypervascularized and there was a slight, nonsignificant increase in tumor diameter. As TACE had not been effective and poorly tolerated and the patient was not a good candidate for surgery, he was offered SIRT.

In September 2009, SIRT with 1923 MBq was performed, treating the tumor selectively. The procedure was well tolerated. The patient was reevaluated every 3 months. He had stable disease and a good performance status for 3 years. In October 2012, he developed progressive disease with a deterioration of liver function, which prevented further treatment.

**Case history 5**
Presentation & clinical history
A 78-year-old male presented with moderately differentiated G2 HCC in the right lobe (dimensions: 10.5 × 15 cm), which was confirmed on biopsy (Figure 5). α-fetoprotein levels were at 2.1 ng/ml. He had no concomitant liver disease.

Treatment & outcomes
Six sessions of TACE were performed over 1 year. Two months after the last TACE session, progressive disease was identified. After two sessions of SIRT (performed at 3 and 4 months after TACE on the right and left liver lobe), the disease stabilized until disease progression was treated with sorafenib at 6 months after SIRT.

**Discussion**
In case 4, TACE was considered to be an appropriate first-line treatment before SIRT because the tumor was highly vascularized. If the tumor had been hypoperfused, other treatments would have to be considered. In our experience, patients who do not tolerate TACE are generally not good candidates for subsequent surgery, especially if their liver function deteriorates.

In case 5, it was difficult to determine whether the patient benefited from TACE, as the tumor biology may have been nonaggressive. Several centers withhold TACE if there is no clear evidence of a response after two sessions. After six sessions of TACE, it is very important to re-evaluate the status of the hepatic arteries on angiography before proceeding with secondary SIRT. Although there is no clear evidence from prospective studies of the value of SIRT after TACE, our experience with SIRT means that we would consider this procedure in this setting.

**Conclusion**
In our opinion, SIRT is an appropriate option for the treatment of large tumors with or without...
portal vein infiltration. Simultaneous treatment with sorafenib and TACE is not recommended; however, interim evidence (from SORAMIC) suggests that the combination of SIRT and sorafenib is well tolerated [16] and further data on the efficacy of this combination will be available in 2015. The multimodal treatment of patients with advanced HCC (with locoregional treatment and surgery) is a new and promising field of investigation since SIRT is able to induce a complete response even in advanced, infiltrative HCC with vascular invasion; however, the evaluation of the response using imaging alone remains a challenge. In selected cases with preserved liver function, SIRT may be an option for the management of tumor progression or in patients who are unable to tolerate TACE. SIRT should also be considered to be the option of choice when drug-eluting beads-TACE fails to halt disease progression.

Financial & competing interests disclosure
C Verslype has received research funding from Sirtex Medical. FT Kolligs has received honoraria from Sirtex Medical and Bayer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References
1 Greten TF, Malek NP, Schmidt S et al. [Diagnosis of and therapy for hepatocellular carcinoma]. Z. Gastroenterol. 51(11), 1269–1326 (2013).
11 Piscaglia F, Bolondi L. The intermediate hepatocellular carcinoma stage: should treatment be expanded? Dig. Liver Dis. 42(Suppl. 3), S258–S263 (2010).
SIRT in challenging cases of liver-predominant unresectable hepatocellular carcinoma

**SYMPOSIUM PAPER**


34 Kalva SP, Pectasides M, Lui R et al. Safety and effectiveness of chemoembolization with drug-eluting beads for advanced-stage hepatocellular carcinoma.


Breast Cancer Management

AN INDISPENSABLE RESOURCE FOR THE PRACTICING CLINICIAN

"Disseminate the most effective management strategies for this common disease"

Senior Editor Mike Dixon

Email us to set up your FREE TRIAL
trials@futuremedicine.com

www.futuremedicine.com
State of the art: colorectal liver metastases

Alberto Sobrero*1 & Alessandro Pastorino1

In the last 10 years, the medical treatment of advanced colorectal cancer has evolved to include a complex combination of chemotherapy protocols with new biological agents.

Integrating medical treatment & surgery
Four clinical conditions can be identified for the integration of medical treatment and surgery for patients with colorectal liver metastases: adjuvant treatment post-R0 resection; neoadjuvant treatment for resectable disease; conversion from potentially resectable to resectable disease; and palliative treatment (including liver-directed therapies) for unresectable liver-dominant disease.

• Adjuvant treatment post-R0 resection
The efficacy of pure adjuvant chemotherapy in stage 4 disease is debatable. Certainly, the benefit of adjuvant chemotherapy in stage 4 disease appears to be less than that observed with adjuvant chemotherapy in stage 3 disease. Data from a meta-analysis showed that fluorouracil (FU) afforded a borderline significant benefit in terms of recurrence-free survival compared with surgery alone [1], while folinic acid (leucovorin), 5-fluorouracil (5-FU), irinotecan (FOLFIRI) produced a numerically better recurrence-free survival than FU, but this difference was not statistically significant [2]. Importantly, folinic acid (leucovorin), 5-FU, oxaliplatin (FOLFOX) has not been studied in this setting, although it is the regimen that is most commonly employed in clinical practice around the world.

• Neoadjuvant chemotherapy of resectable metastases
‘Neoadjuvant chemotherapy’ of resectable metastases has only been investigated as a ‘perioperative strategy’ (i.e., as part of a strategy in which chemotherapy is continued after surgery). A systematic review of 23 neoadjuvant chemotherapy trials for resectable colorectal liver metastases reported a median response rate of 64% (leading to a 93% R0 resection rate) and a median disease-free survival of 21 months [3]. The European Organisation for Research and Treatment of Cancer (EORTC) conducted the only randomized controlled Phase III study comparing perioperative chemotherapy (six cycles of FOLFOX before and six cycles after surgery) versus surgery alone. This study found that the absolute increase in the rate of progression-free survival at 3 years was only 7.3% (from 28.1% [95.66% CI: 21.3–35.5] to 35.4% [95.66% CI: 28.1–42.7]; HR: 0.79 [95.66% CI: 0.62–1.02]; p = 0.058) [4], with a non-significant difference in overall survival at 5 years of follow-up (HR: 0.88; 95% CI: 0.68–1.14; p = 0.339) [5]. Last year, the New EPOC study investigated the addition of adjunct cetuximab to FOLFOX perioperative chemotherapy in K-RAS-wild-type patients [6]. This study unexpectedly found that the addition of the cetuximab had a detrimental effect on survival compared with FOLFOX alone in the neoadjuvant setting (14.8 vs 24.2 months; HR: 1.5; 95% CI: 1.0–2.2; p < 0.048).
### Conversion to resectable disease

With the advent of more active combination chemotherapies (compared with FU alone), a number of studies have reported resections of unresectable liver metastases [7–9]. Since then, disease downstaging has become the key end point of ‘conversion therapy’ studies. However, while the goal of downstaging from potentially resectable to resectable R0 disease is highly desirable, in reality, the only clinically relevant end point for the patient is R0 disease that lasts at least 6–12 months postresection, but this end point has never been assessed. In nonresectable metastases, a study by Tournigand et al. reported higher response rates for FOLFOX, with corresponding R0 resection rates of 22 compared with 9% with FOLFIRI [10]. In two randomized Phase III trials, Falcone et al. demonstrated an increased response rate and R0 resection rate for the triplet regimen 5-FU/folinic acid, oxaliplatin and irinotecan (FOLFOXIRI) (± bevacizumab) compared with FOLFIRI (± bevacizumab) [11,12]. These data were not confirmed in a similar randomized study from Greece [13], but were corroborated in the most recent OLIVIA study where FOLFOXIRI–bevacizumab was compared with mFOLFOX6–bevacizumab in patients with unresectable liver metastases [14]. At least three studies have shown consistent improvements in response rates (ranging from 59 to 79%) with the addition of cetuximab to chemotherapy in K-RAS-wild-type tumors [15–17], and despite the New EPOC study results, this anti-EGFR compound (in combination with FOLFIRI) has made an important contribution to enhancing resectability rates. The NO16966 trial, which compared capecitabine plus oxaliplatin (XELOX)/FOLFOX with or without bevacizumab, demonstrated a nonstatistically significant increase in the resection rate with bevacizumab (17.1 vs 12.6% for patients with liver-only metastases) [18]. The OLIVIA study (mentioned above) also served to enhance the credibility of bevacizumab in this setting. When considering which biological agent may be the best in terms of enhancing the tumor shrinkage effects of chemotherapy, there are no clear answers, thereby confounding the interpretation of these data (Figure 1). Moreover, while FOLFOXIRI with or without bevacizumab is highly effective as a conversion therapy, in the hands of inexperienced oncologists, it is associated with unacceptably high grade 3–4 rates of diarrhea (in up to 28% of cases) [14].

Recently, locoregional treatment with hepatic artery infusion combined with systemic doublet

#### Figure 1. Tumor shrinkage: incremental response rates with biologicals in randomized trials.


<table>
<thead>
<tr>
<th>Bevacizumab</th>
<th>Incremental response rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVF2107g IFL</td>
<td>+10%</td>
</tr>
<tr>
<td>E3200I line FOLFOX</td>
<td>+12%</td>
</tr>
<tr>
<td>NO16966</td>
<td>0%</td>
</tr>
<tr>
<td>MAX2010</td>
<td>+7%</td>
</tr>
<tr>
<td>AVEX 2013</td>
<td>+9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cetuximab</th>
<th>K-RAS WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal FOLFIRI</td>
<td>+18%</td>
</tr>
<tr>
<td>OPUS FOLFOX</td>
<td>+23%</td>
</tr>
<tr>
<td>COIN FOLFOX XELOX</td>
<td>+7%</td>
</tr>
<tr>
<td>NORDIX FLOX</td>
<td>0%</td>
</tr>
<tr>
<td>FIRE III</td>
<td>+4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Panitumumab</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME FOLFOX</td>
<td>+9%</td>
</tr>
<tr>
<td>181 II LINE FOLFIRI</td>
<td>+25%</td>
</tr>
<tr>
<td>PICCOLO IRI</td>
<td>+22%</td>
</tr>
</tbody>
</table>
chemotherapy has proved to be extremely efficacious as a conversion therapy [19], although the key limitations to this approach continue to be the lack of widespread experience with this therapy, as well as the toxicity associated with systemic oxaliplatin–irinotecan and the high complication rates associated with the catheters and implanted pumps. In order to provide some clarity on this complex issue, a tentative classification of the relative risks/benefits of various conversion therapies is provided in Figure 2.

- Palliative treatment (including liver-directed therapies) for unresectable liver-dominant disease

Advances in systemic therapy and the potential impact of these therapies on the biology of advanced colorectal cancer have served to enhance patient survival to between 24 and 34 months in appropriately selected patients. This has provided a meaningful window for the improved management of the liver metastases (even in the context of disseminated disease). Resection of liver-limited metastases and locoregional infusion of irinotecan-loaded beads (DEBIRI) [20] and selective internal radiation therapy (SIRT; also known as radioembolization) with yttrium-90 microspheres [21,22] have been proposed for the management of liver-dominant disease. In a study of 44 patients with liver-only disease, Hendlisz et al. found that patients who received SIRT with Y-90 resin microspheres plus FU significantly benefited from a longer time to progression of target liver lesions compared with FU alone (5.5 vs 2.1 months), even in the chemotherapy-refractory setting [23]. Without control of the systemic disease, however, this approach may not be warrant, but whenever the extrahepatic disease has an indolent clinical course, these strategies may afford substantial clinical benefits in selected patients. In this respect, it will be particularly interesting to see the results of the combined analysis of randomized studies in more than 1000 patients, which will compare FOLFOX with or without the addition of SIRT with Y-90 resin microspheres. Despite the inherent difficulties in conducting such trials (with a potential internal bias associated with the selection of patients), these trials are needed in order to understand the true value and role of liver-directed treatments in the management of liver-dominant metastatic disease.

Financial & competing interests disclosure

A Sobrero has received honoraria for advisory board activities as well participation in satellite symposia as a speaker for Roche, Sanofi, Merck, Bayer and Amgen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

Figure 2. Summary of the relative benefits of various conversion therapies.

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hai</td>
<td>+++++</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>+++</td>
</tr>
<tr>
<td>FOLFOXIRI bevacizumab</td>
<td>+++</td>
</tr>
<tr>
<td>FOLFIRI cetuximab</td>
<td>+/(+)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>++</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>+(+)</td>
</tr>
</tbody>
</table>

Table 3: Summary of the relative benefits of various conversion therapies.

Advances in systemic therapy and the potential impact of these therapies on the biology of advanced colorectal cancer have served to enhance patient survival to between 24 and 34 months in appropriately selected patients. In this respect, it will be particularly interesting to see the results of the combined analysis of randomized studies in more than 1000 patients, which will compare FOLFOX with or without the addition of SIRT with Y-90 resin microspheres. Despite the inherent difficulties in conducting such trials (with a potential internal bias associated with the selection of patients), these trials are needed in order to understand the true value and role of liver-directed treatments in the management of liver-dominant metastatic disease.

Financial & competing interests disclosure

A Sobrero has received honoraria for advisory board activities as well participation in satellite symposia as a speaker for Roche, Sanofi, Merck, Bayer and Amgen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References


21 Official SIRFLOX study website. www.sirfox.com


Evidence-based integration of selective internal radiation therapy in the management of colorectal liver metastases

Harpreet S Wasan*

There is an inherent bias among interventional radiologists that consolidation therapies, such as selective internal radiation therapy (SIRT), have value in the management of chemotherapy-refractory disease. In the same way, surgeons may believe that they are able to cure patients who have liver-dominant metastatic colorectal cancer, but in reality, this occurs only in a minority of patients with perioperative chemotherapy [1,2]. Even in patients with classically resectable liver disease (i.e., fewer than three to four liver metastases; classified as category “A” in this article; Figure 1) who received neo-adjuvant chemotherapy with folic acid (leucovorin), fluorouracil (5-FU), oxaliplatin (FOLFOX4) followed by R0 resection, the relapse rates are surprisingly high (50% within 14–18 months).

Clinical framework for the management of metastatic colorectal cancer

Until answers can be found for the better predictive characterization of the molecular features of cancers, the management of cancer has to be considered in a clinical framework with three broad clinical categories (as proposed here in Figure 1 for metastatic colorectal cancer).

For category A patients who received R0 resection of liver metastases, the European Organisation for Research and Treatment of Cancer (EORTC) 40983 Intergroup recently reported median overall survivals of 54–63 months with a 5-year survival rate of approximately 50% [1]. The most common clinical presentation of advanced colorectal cancer, however, is category C, in which patients have at least two separate organ metastatic sites (many may still have liver dominance). For these patients, overall survival is between 18 and 25 months, plus an additional 5–7.5 months in selected patients (KRAS/NRAS all wild-type) [3] and (worse) minus approximately 5 months in BRAF-mutant patients [4]. The intermediate category B patients have four or more liver metastases and no obvious systemic disease. Randomized surgical trials in this subgroup are lacking and there is no consensus on which patients are ‘potentially operable’; most of these patients will have micrometastases within and beyond the liver, which cannot be detected by current imaging modalities. By definition, these patients have a worse prognosis than category A patients as observed in the CELIM study [5] and the provisional analysis from the New EPOC study [6]. In patients with more than five metastases at baseline, disease-free survival was only 9.9 months (95% CI: 5.8–14.0) after R0 resection [5]. These data indicate that patients presenting with more than five metastases, even if they were candidates for ‘downstaging’ with chemotherapy and subsequent resection, relapse at a suboptimal period. There remains a high medical need to improve 5-year outcomes in category B patients, using either: the addition of biologic therapies to standard chemotherapy regimens (as discussed by Sobrero and Pastorino in this supplement); liver-directed locoregional therapies, such as embolization (bland/transarterial embolization [TAE]), hepatic artery or portal vein infusion of cytotoxic agents or SIRT; or direct treatment of visually targeted tumors using ablation, NanoKnife® (AngioDynamics, NY, USA), (IRE) irreversible electroporation or external beam radiotherapy: stereotactic body radiation therapy (SBRT) as well...
Figure 1. Categorization of patients with colorectal liver metastases.

- **Category A**: localized <3–4 liver metastases
  - Operable/surgical ‘cure’

- **Category B**: 4+ liver metastases with no obvious systemic disease

- **Category C**: Systemic disease ‘incurable’ with liver metastases

More unselected systemic therapy is associated

Figure 2. Integrating selective internal radiation therapy into the metastatic colorectal cancer treatment paradigm.
Evidence-based integration of SIRT into the management of colorectal liver metastases

SYMPOSIUM PAPER

with more side effects and rarely leads to complete responses; direct treatment of visually targeted liver lesions is not possible and thus ineffective for the management of micrometastases. There is encouraging evidence suggesting that there might be a potential synergy between the use of locoregional approaches and systemic therapy in order to improve outcomes in these patients [7,8]. With internal radiation (i.e., SIRT), it may be that the radiation cloud, which is associated with the distribution of yttrium-90 resin microspheres around the perimeter of the growing tumor(s), may have cytotoxic effects on nearby small (<1 mm), avascular micrometastases, which cannot be targeted by systemic therapies.

There is a suggestion from the CLOCC trial that radiofrequency ablation following chemotherapy in order to debulk the liver of tumor had a beneficial effect on outcome [7]. Similarly, in a randomized study, Hendlitz et al. showed that the addition of SIRT with Y-90 resin microspheres to FU in the chemotherapy-refractory setting impacted on both the subsequent development of metastases in the liver and also, surprisingly, outside the liver [7]. There is also good evidence that progression-free survival diminishes significantly with each line of therapy [10–14] and so (in theory) patients who received locoregional therapies are likely to derive the greatest benefit from such treatments in the first-line setting.

Conclusion
The evidence from many large case series, Phase II studies and one Phase III study provides a promising confirmation of the efficacy and safety of SIRT with Y-90 resin micropheres. For this reason, SIRT is now being investigated across a range of treatment settings in prospective, randomized, Phase II/III trials in order to evaluate its impact on the outcomes of patients with advanced colorectal cancer and other cancers (Figure 2).

Financial & competing interests disclosure
HS Wasan has the following disclosures: Sirtex Medical Ltd, Merck KGA and Pfizer (advisory board member/speaker and research funding); Sanofi Aventis, Roche and Bayer (advisory board member/speaker); and CRUK, MRC and BRC-Imperial (research funding). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobby (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References
3 Stintzing S, Jung A, Rossius L. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: a randomized Phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. http://2013.europeanacancercongress.org


Ongoing selective internal radiation therapy-based studies in the treatment of liver-dominant metastatic colorectal cancer

Volker Heinemann*

Selective internal radiation therapy (SIRT; also known as radioembolization) combined with systemic chemotherapy is an investigational treatment that, compared with chemotherapy alone, has been shown to improve local control (response rate as measured by Response Evaluation Criteria In Solid Tumors [RECIST] version 1.0) and survival in patients with liver-dominant metastatic colorectal cancer in prospective studies (Table 1) [1–5].

Ongoing randomized controlled trials
There are currently three Phase III, large, multicenter trials ongoing in order to evaluate the safety and efficacy of combining systemic chemotherapy with SIRT (using yttrium-90 resin microspheres: SIR-Spheres®, Sirtex Medical Ltd, Sydney, Australia) versus chemotherapy alone in the first-line setting for inoperable metastatic colorectal cancer (Table 2): SIRFLOX (SIR-Spheres + modified FOLFOX6 [± bevacizumab] versus modified FOLFOX6 [± bevacizumab]) [6]; 5-fluorouracil, oxaliplatin and folinic acid ± interventional radioembolization (FOXFIRE) in the UK [7,8]; and FOXFIREGlobal [9]. These trials allow the inclusion of limited extrahepatic disease; for example, patients can be included in the SIRFLOX study with either five or fewer lung metastases of ≤1 cm or one metastasis of ≤1.7 cm and/or lymph nodes <2 cm if in one region.

The primary end points are progression-free survival (for SIRFLOX) and overall survival (for FOXFIRE and FOXFIREGlobal). Other end points include safety, response and other key healthcare outcomes, including resection rate (SIRFLOX), costs/health economics (FOXFIRE) and interval from randomization to start of second-line treatment (FOXFIRE).

Patient recruitment into the SIRFLOX study started in 2006 and ended in April 2013, with results on the primary end point expected to be presented in 2015. Patient recruitment into the FOXFIRE study started in February 2010 and is expected to end by Q4 2014. Results on the primary end point are expected to be presented during 2016. FOXFIREGlobal, involving centers in Australia, New Zealand, Asia, Europe, Israel and the USA, will continue to recruit patients until the combined number of patients recruited across all three trials (SIRFLOX + FOXFIRE + FOXFIREGlobal) has reached at least 1022 patients. The end point of the combined analysis will be overall survival; the results are not expected to be presented before 2016.

In the UK, running in parallel with FOXFIRE is a pilot study (PERFORM) that is investigating the feasibility and usefulness of performing a novel computed tomography (CT) scanning technique called perfusion CT as an addition to normal CT scanning. All patients recruited to FOXFIRE at the Oxford Radcliffe Hospitals (UK) and University Hospitals of Leicester (UK) will be invited to take part.

Another smaller trial, SIRSTEP, is evaluating SIRT with Y-90 resin microspheres as a first-line maintenance or consolidation therapy in combination with leucovorin/5-fluorouracil (LV5/FU)

*University of Munich – Klinikum der Universitaet Muenschen Comprehensive Cancer Center – Krebszentrum Muenchen CCCLMU, Marchioninistrasse 15, D – 81377 Munich, Germany; volker.heinemann@med.uni-muenchen.de

KEYWORDS
• liver
• metastatic colorectal cancer
• selective internal radiation therapy
• treatment
(± bevacizumab) versus LV5/FU (± bevacizumab) alone (Figure 1). In the USA, SIRT is being evaluated prospectively in patients who have failed prior intra-arterial infusion therapy. Finally, the EXPLOSIVE study is evaluating the predictive value of technetium-radiolabeled, macroaggregated human serum albumin scintigraphy to response to SIRT.

### Table 1. Summary of published prospective studies with selective internal radiation therapy with Y-90 resin microspheres in combination with systemic chemotherapy in unresectable liver-dominant metastatic colorectal cancer.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Therapy</th>
<th>Patients (n)</th>
<th>ORR (%)</th>
<th>Median TTP or PFS (months)</th>
<th>p-value</th>
<th>Median survival (months)</th>
<th>p-value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray <em>et al.</em> (2001)</td>
<td>SIRT + FUDR-HAC</td>
<td>36</td>
<td>44</td>
<td>15.9*</td>
<td>39% at 2 years</td>
<td></td>
<td></td>
<td>[1]</td>
</tr>
<tr>
<td></td>
<td>FUDR-HAC</td>
<td>34</td>
<td>18</td>
<td>9.7</td>
<td>29% at 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Hazel <em>et al.</em> (2004)</td>
<td>SIRT + 5-FU/LV</td>
<td>11</td>
<td>90.1</td>
<td>18.6*</td>
<td>&lt;0.0005</td>
<td>29.4</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-FU/LV</td>
<td>10</td>
<td>0.0</td>
<td>3.6*</td>
<td></td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma <em>et al.</em> (2007)</td>
<td>SIRT + FOLFOX</td>
<td>20</td>
<td>90.0</td>
<td>9.3 (14.2 liver only)</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Hazel <em>et al.</em> (2009)</td>
<td>SIRT + irinotecan</td>
<td>25</td>
<td>48.0</td>
<td>6.0 (9.2 liver only)</td>
<td>12.2</td>
<td></td>
<td></td>
<td>[4]</td>
</tr>
<tr>
<td><strong>Salvage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hendisz <em>et al.</em> (2010)</td>
<td>SIRT + 5-FU</td>
<td>21</td>
<td>0</td>
<td>4.5 (5.5 liver only)</td>
<td>0.003</td>
<td>10.0</td>
<td>NS</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>5-FU (+ SIRT at progression</td>
<td>23</td>
<td>0</td>
<td>2.1</td>
<td></td>
<td>7.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in ten patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value SIRT-based therapy versus comparator.
5-FU: 5-fluorouracil; FOLFOX: Folinic acid (leucovorin), fluorouracil plus oxaliplatin; FUDR-HAC: Floxuridine-hepatic artery chemotherapy; LV: Leucovorin; NR: Not reported; NS: Not significant; ORR: Overall response rate; PFS: Progression-free survival; SIRT: Selective internal radiation therapy; TTP: Time to progression.

Finally, the EXPLOSIVE study is evaluating the predictive value of technetium-radiolabeled, macroaggregated human serum albumin scintigraphy to response to SIRT.

---

Figure 1. SIRSTEP: first-line consolidation therapy (principal investigators: M Peeters [Antwerp University Hospital, Antwerp, Belgium] and M van den Eynde [Jules Bordet Institute, Brussels, Belgium]). The subscripts denote the first and second measures of time to progression, which combined provide the overall TTP.

5-FU: 5-fluorouracil; Beva: Bevacizumab; CT: Computed tomography; mCRC: Metastatic colorectal cancer; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TTP: Time to progression.
Ongoing SIRT-based studies in the treatment of liver-dominant metastatic colorectal cancer

**SYMPOSIUM PAPER**

### Table 2. Summary of ongoing selective internal radiation therapy studies in metastatic colorectal cancer.

<table>
<thead>
<tr>
<th>Status</th>
<th>Trial</th>
<th>Clinicaltrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active, not recruiting</td>
<td>SIRFLOX: mFOLFOX6 (± Bev) + SIRT vs mFOLFOX6 (± Bev) in patients with inoperable liver metastases; international study sponsored by SIRTEX</td>
<td>NCT00724503</td>
</tr>
<tr>
<td>Recruiting</td>
<td>FOXFIRE: OxMdG + SIRT vs OxMdG in patients with inoperable liver metastases; UK trial sponsored by the University of Oxford</td>
<td>ISRCTN83867919</td>
</tr>
<tr>
<td>Recruiting</td>
<td>FOXYFIREGlobal (similar design to SIRFLOX)</td>
<td>NCT01721954</td>
</tr>
<tr>
<td>Active, not recruiting</td>
<td>SIRSTEP: first-line maintenance/consolidation with SIRS + LV5/FU (± Bev) vs LV5/FU (± Bev) alone</td>
<td>NCT01895257</td>
</tr>
<tr>
<td>Active, not recruiting</td>
<td>SIRT in patients who failed prior intra-arterial pump therapy</td>
<td>NCT00972036</td>
</tr>
<tr>
<td>Recruiting</td>
<td>PERFORM: perfusion CT in the FOXYFIRE trial in order to study blood flow to liver metastases</td>
<td>NCT01410760</td>
</tr>
<tr>
<td>Active, not recruiting</td>
<td>EXPLOSIVE: predictive value of technetium-radiolabeled, macroaggregated human serum albumin scintigraphy before SIRT</td>
<td>NCT01186263</td>
</tr>
</tbody>
</table>

From clinicaltrials.gov.
International Standard Randomized Controlled Trial Number Register.

mFOLFOX6 and OxMdG are chemotherapy regimens combining oxaliplatin with fluorouracil (5-FU) and folinic acid (leucovorin).
Bev: Bevacizumab; CT: Computed tomography; LV5/FU: Leucovorin/5-fluorouracil; SIRT: Selective internal radiation therapy.

**Financial & competing interests disclosure**

V Heinemann has received research funding as well as grants for travel and talks from Sirtex Medical Ltd. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

**References**

6 FOLFOX Plus SIR-Spheres Microspheres Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer (SIRFLOX) (NCT00724503). www.sirfox.com
7 NICE. Interventional procedure guidance 401: selective internal radiation therapy for non-resectable colorectal metastases in the liver. www.nice.org.uk
8 Oncology Clinical Trials Office (OCTO). www.octo-oxford.org.uk
9 Roswell Park Cancer Institute. (FOXYFIRE Global STX0112) Assessment of Overall Survival of FOLFOX6m Plus SIR-Spheres Microspheres Versus FOLFOX6m Alone as First-Line Treatment in Patients with Non-Resectable Liver Metastases from Primary Colorectal Carcinoma in a Randomized Clinical Study (NCT01721954). www.roswellpark.org
Lung Cancer Management addresses key issues and current understanding in the diagnosis, staging and treatment of disease by exploring the best patient-centered clinical research and presenting this information both directly, as clinical findings, and in practice-oriented formats of direct relevance in the clinic.

Email us today for your FREE TRIAL

Future Medicine

trials@futuremedicine.com
www.futuremedicine.com

Citations:
Chemical Abstracts
EMBASE/Excerpta Medica
Case histories in unresectable liver-dominant metastatic colorectal cancer

Ricky A Sharma*,1, Marc Peeters2 & Julien Taïeb3

The most common cause of death from advanced colorectal cancer is disease progression of hepatic metastases. Selective internal radiation therapy (SIRT) is a technique for administering resin or glass microspheres that contain yttrium-90 to unresectable primary or secondary hepatic malignancies via the liver’s arterial supply in a single procedure.

Chemoradiation studies suggest that the greatest clinical benefit from yttrium-90 microsphere SIRT is gained by rational combination with radiosensitizing systemic chemotherapy (Figure 1) [1,2] in order to achieve both temporal modulation and biological cooperation between these treatment modalities. There is an established evidence base for rational combinations of SIRT with fluoropyrimidine-, oxaliplatin- and irinotecan-based regimes, based on radiobiological principles [3–5]. In particular, patients who cannot tolerate infusional 5-fluorouracil (5-FU) or capecitabine who have liver-only or liver-dominant metastatic disease should be considered for SIRT [6,7].

Detailed histological analysis of the liver tissue in patients resected 4–9 months after chemotherapy and SIRT shows that a complete pathological response can be achieved. Furthermore, fibrosis, ectatic vessels and vascular changes were predominantly observed (i.e., histological evidence of a direct local radiotherapy effect), rather than a cellular inflammatory response (which would be suggestive of histopathological changes induced by embolization or by chemotherapy; Figure 2) [6].

Consolidation treatment for patients after first-line chemotherapy
Consolidation treatment is used after patients have achieved a good response to first-line therapy for inoperable metastatic colorectal cancer (mCRC). At this time point, patients are switched to an alternative (consolidation) treatment in order to reinforce the treatment response and to maintain health-related quality of life (HRQoL) in the palliative setting.

Case history 1
A 60-year-old female patient with no family history of colon cancer presented in August 2010 with adenocarcinoma of the descending colon with liver (and possibly lung) metastases that were not resectable; carcinoembryonic antigen levels were not elevated (0.7 μg/l). Biomarker analysis revealed a KRAS exon 2 mutation; the descending colon was stented and systemic therapy was initiated with infusional p < 0, folinic acid and oxaliplatin (FOLFOX6). In November 2010, the patient had stable disease, but after stent restenosis with clinical subobstruction, the primary lesion was resected (R0 resection) and the patient proceeded to receive treatment with FOLFOX6. Four months after initiating FOLFOX6 (in January 2011), a partial response of the liver lesions was detected on PET/computed

KEYWORDS
• chemotherapy-refractory
• colorectal cancer
• consolidation treatment
• liver metastases • second-line • selective internal radiation therapy
### Figure 1. Radiosensitizing properties of drugs for metastatic colorectal cancer.
Based on information from [21].

<table>
<thead>
<tr>
<th>Drug</th>
<th>DNA Damage</th>
<th>DNA Repair</th>
<th>Cell Cycle</th>
<th>Apoptosis</th>
<th>Tumor Vasculature</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-fluorouracil</td>
<td>Induction of DNA DSBs</td>
<td>Inhibition of DSB repair</td>
<td>Elimination of S phase cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Inhibition of topoisomerase I</td>
<td>Elimination of S phase cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Formation of DNA adducts</td>
<td>Inhibition of DSB repair</td>
<td>Arrest in G2/M and S phases</td>
<td>PS3-independent cell kill</td>
<td>Normalization of vasculature</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Acute suppression of DNA-PK activity</td>
<td>Accumulation in G1 and G2</td>
<td>Effects on bax and bcl-2</td>
<td>Inhibition of VEGF release</td>
<td></td>
</tr>
</tbody>
</table>

Factors influencing radiosensitization:
- Apoptosis
- Permanent arrest
- Mitotic catastrophe

**Discussion**

In unresectable patients, both the COIN [10] and GERCOR OPTIMOX2 [11] studies have shown that intermittent and continuous consolidation therapy have similar outcomes. However, the CAIRO3 study of 558 patients with mCRC recently determined a modest but significant improvement in overall survival (21.7 vs 18.2 months) if patients continued with maintenance therapy with capecitabine and oxaliplatin (CAPEX/XELOX) plus bevacizumab rather than discontinuing therapy (with its reintroduction after progression) in patients who had an initial minimum response (stable disease) after six cycles of CAPOX plus bevacizumab [12]. However, in the future, consolidation therapy with chemotherapy plus SIRT may also be an option, and one such trial (Sirstep; NCT01895257), which will evaluate the impact of this procedure with chemotherapy (± bevacizumab) on time to progression, overall survival and HRQoL compared with chemotherapy (± bevacizumab) alone is ongoing (Box 1). Alternatively, the FOCUS4 study is evaluating the impact of patient selection for standard and novel therapies by molecular profile in patients with mCRC not necessarily confined to the liver [13].

**Yttrium-90 microspheres as a second-line therapy for mCRC**

Clinical trials of SIRT with concomitant radiosensitizing chemotherapy have shown that...
this combined multidisciplinary approach can be used in second-line therapy, with promising results in patients with mCRC. In some cases, SIRT plus systemic chemotherapy can render initially unresectable liver metastases amenable to potentially curative surgery or ablation [3,6] or be associated with a sustained long-term response not usually observed with chemotherapy alone [3].

● Case history 2
A 51-year-old woman with no comorbidities presented with a stenosing adenocarcinoma of the proximal sigmoid colon and acute intestinal obstruction and synchronous liver metastases. The patient underwent a Hartmann’s resection. Histopathology revealed a pT4bpN2 tumor with vascular invasion (tumor markers: *KRAS* wild-type, *BRAF* wild-type and microsatellite stable). After one cycle of FOLFOX chemotherapy, she was admitted to a coronary care unit on day 2 with acute coronary syndrome and the infusional 5-FU was stopped (coronary complications are a serious and relatively common adverse event, observed in between 2 and 12% of patients treated with infusional 5-FU). In such cases, raltitrexed-based regimens are one alternative to 5-FU-based regimens [14] or cetuximab plus irinotecan-based chemotherapy in *KRAS*-wild-type mCRC [15]. Alternatively, for those patients who do not wish to receive further systemic chemotherapy immediately, SIRT is a potential treatment option to consider in liver-only or liver-dominant disease after full staging by PET/computed tomography. This patient decided to have SIRT, followed by six cycles of irinotecan plus cetuximab and, following a partial response 8 months after SIRT, proceeded to a left hepatectomy and segment 6 resection. This multimodal approach was offered because there is evidence that an initial R0 resection is associated with a longer overall survival. Four months after liver surgery, and 2 years after diagnosis, a new liver metastasis (~4 cm in diameter) was observed in segment 8. The patient received thermal ablation of the metastases in segments 4 and 7. Almost 3 years from initial presentation and SIRT, PET scan showed FDG-avid nodules in the lung and right iliac fossa and further systemic therapy was initiated.
Box 1. Eligibility for the SIRSTEP trial (NCT01895257).

Inclusion criteria

- Willing and able to provide written informed consent
- Histologically confirmed adenocarcinoma of the colon or rectum, with or without primary tumor in situ. Unequivocal and measurable (RECIST version 1.1) CT evidence of liver metastases that are not treatable by surgical resection and/or local ablation with curative intent at the time of trial entry
- Partial response or stable disease (RECIST version 1.1 criteria, controlled metastatic disease) after chemotherapy induction with oxaliplatin- or irinotecan-based induction chemotherapy (FOLFOX, FOLFIRI or XELOX) ± bevacizumab over 3 months
- At least one of all of the measurable liver metastases must present FDG uptake at the PET scan performed before inclusion (3 months after chemotherapy induction). FDG-PET-positive liver metastasis is defined by an FDG uptake ≥1.5-times the uptake of the surrounding nontumoral liver parenchyma
- Limited extrahepatic metastases in the lung and/or lymph nodes are permitted. Metastases in the lung must either be not more than five nodules in number with no individual nodule more than 1 cm in diameter or one single lesion of up to 1.7 cm in diameter. Involvement of lymph nodes in one single anatomic region (pelvis, abdomen or chest) are permitted provided that their longest diameter measures less than 2 cm
- All imaging evidence used as part of the screening process must be within 28 days prior to the time of randomization
- Suitable for either treatment regimen as determined by clinical assessment undertaken by the investigator
- Patients may have received adjuvant chemotherapy or (neo-)adjuvant chemoradiotherapy to the pelvis, provided that the last dose of chemotherapy was administered at least 6 months prior to begin chemotherapy induction. Previous radiotherapy to the pelvis is not an exclusion criterion
- WHO performance status 0–1

Adequate hematological, renal and hepatic function

- Hematological neutrophils >1.5 × 10⁹/l; platelets >100 × 10⁹/l; renal creatinine <1.5 × ULN; hepatic bilirubin ≤1.0 × ULN; albumin ≥30g/l; ALT ≤5.0 × ULN; AST ≤5.0 × ULN; LDH ≤2.5 × ULN; the date of blood tests must be within 28 days prior to the time of randomization
- Age 18 years or older
- Female patients must either be postmenopausal, sterile (surgically or radiation or chemically induced) or, if sexually active using, be using an acceptable method of contraception
- Male patients must be surgically sterile or, if sexually active and having a premenopausal partner, must be using an acceptable method of contraception
- Life expectancy of at least 3 months without any active treatment
- Minimum and maximum administered cycles of induction chemotherapy before trial inclusion (date of signed informed consent) should be: XELOX – three to five cycles; FOLFOX/FOLFIRI – four to seven cycles

Exclusion criteria

- The patient is not eligible for the trial if the metastatic colorectal cancer does not have any FDG uptake at diagnosis before chemotherapy induction (for the definition of FDG uptake, see the above inclusion criteria)
- Evidence of ascites, cirrhosis, portal hypertension, main portal venous tumor involvement or thrombosis as determined by clinical or radiological assessment
- Previous radiotherapy delivered to the upper abdomen
- Nonmalignant disease that would render the patient unsuitable for treatment according to this protocol
- Prior major liver resection: remnant liver ≤50% of the initial liver volume. Patients with a biliary stent can be included
- Liver tumor involvement >80%
- Resectable metastatic disease
- Progressive disease during first-line metastatic chemotherapy
- Utilization of cetuximab or panitumumab during the chemotherapy induction period
- Concomitant utilization of oxaliplatin and irinotecan during the chemotherapy induction period (FOLFOXIRI regimen)
- Contraindication to further reintroduction of oxaliplatin (allergy or permanent grade 2/3 neurotoxicity)
- Pregnant or breast feeding
- Concurrent or prior history of cancer other than adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix
- Allergy to nonionic contrast agents
- The period between day 1 of the first induction chemotherapy cycle after disease diagnosis and inclusion (date of signed informed consent) must not exceed 4 months

ALT: Alanine transaminase; AST: Aspartate aminotransferase; CT: Computed tomography; FDG: Fluorodeoxyglucose; FOLFIRI: Infusional 5-fluorouracil with folinic acid and irinotecan; FOLFOX: Infusional 5-fluorouracil with folinic acid and oxaliplatin; FOLFOXIRI: Infusional 5-fluorouracil with folinic acid and oxaliplatin and irinotecan; LDH: Lactate dehydrogenase; RECIST: Response Evaluation Criteria in Solid Tumors; ULN: Upper limit of normal; XELOX: Capecitabine and oxaliplatin.
• **Discussion**  
For those patients who do not wish to receive further systemic chemotherapy or for whom systemic therapy options are limited, SIRT is an important treatment option to consider in liver-only or liver-dominant metastatic disease. Three large-scale Phase III trials – FOXFIRE [16], SIRFLOX [17] and FOXFIREGlobal [18] – are currently testing the hypothesis that the greatest clinical benefit from SIRT may be achieved from this combination therapy at an early time point in a patient’s disease course. These randomized trials have already demonstrated the safety of combining SIRT with concomitant FOLFOX chemotherapy in over 900 patients recruited thus far.

**Chemorefractory mCRC**  
SIRT is also indicated in the salvage setting (Box 2), often in patients with a good performance status despite having progressed on many lines of prior chemotherapy with or without biologicals.

• **Case history 3**  
A 67-year-old male (past smoker) with a medical history of stroke (transient ischemia) in 1992 (was receiving prophylactic aspirin 75 mg/day), hypertension for 10 years (atenolol) and untreated dyslipidemia and a hip replacement in 2003 presented for surgery in June 2008 for a right colonic grade 2 adenocarcinoma pT4aN1b (3N+/11). After adjuvant FOLFOX for 6 months associated with peripheral neuropathy (grade 1 on upper limbs and grade 2 on lower limbs), the patient was lost to follow-up before representing with multiple hepatic metastases on both lobes without extrahepatic disease (on PET/computed tomography) 1 year after the end of adjuvant chemotherapy. The patient was asymptomatic with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, but had lost 4 kg in last 3 months. Serum carcinoembryonic antigen levels were 294 ng/ml; bilirubin was normal and alkaline phosphatase was three-times above the upper limit of normal. As the tumor was characterized as KRAS-wild-type, the patient received infusional p < 0 plus folinic acid plus irinotecan (FOLFIRI) plus cetuximab. An objective response was observed after four cycles (but was still inoperable), and so treatment was continued over a total of 13 months before progression in the liver and the appearance of two lung nodules (9 and 13 mm, respectively). The patient received further FOLFOX plus bevacizumab, which was initially well tolerated and lead to an objective response (-32% on Response Evaluation Criteria In Solid Tumors [RECIST]) at 2 months and stable disease thereafter for 4 months. Oxaliplatin was stopped after seven cycles because of neurotoxicity. Hepatic progression was observed at 6 months, with the lung metastases increasing in size to 12 and 15 mm, respectively. Liver biology was normal and the patient still had a performance status of 1 and had gained 3 kg since the start of treatment. The patient was treated with SIRT. Proton pump inhibitors were administered intravenously for 2 days, then as long-term double dosages in order to avoid upper GI tract side effects. The disease was controlled for 4 months with progression at 6 months, at which time the patient was switched to regorafenib.

• **Discussion**  
What are the options for patients with a good performance status who have been heavily pretreated with approximately all of the available agents & still have liver-dominant disease?  
The evidence for cetuximab rechallenge in the chemorefractory setting is based on only one study including a limited number of patients who were initially progressive on anti-EGFR therapy [19]. Similarly, there is also evidence for regorafenib in this setting [20], but regorafenib is only effective in a subset of patients (still to be defined) and the overall survival benefit was only

---

**Box 2. Patient profile for selective internal radiation therapy in the salvage setting.**

- Unresectable liver-dominant or liver-only disease
- Acceptable life expectancy (>12 weeks)
- Adequate performance status (Eastern Cooperative Oncology Group/WHO: 0–2)
- Resistant to chemotherapy and/or biologicals
- Limited shunting based on macroaggregated albumin scan
- Adequate liver (bilirubin <2 mg/dl), renal (creatinine <25 mg/dl) and marrow function (platelets >60,000/μl, leukocytes >2500/μl and neutrophils >1500/μl)
Figure 3. Progression-free survival with 5-fluorouracil with and without selective internal radiation therapy using Y-90 resin microspheres.
5-FU: 5-fluorouracil; mo: Months.
Based on information from [23].

1.4 months, with tolerability not being optimal at the usual 160 mg/day dose. In this setting, FOLFOX rechallenge is often offered even when there is significant neuropathy, although the evidence for this remains limited. Alternatively, there is randomized trial evidence that 5-FU radiosensitization plus SIRT can extend the time to progression in the liver compared with 5-FU alone in pretreated patients (Figure 3) [4]. For the patient with liver-dominant disease and a reasonable performance status, SIRT would seem to be an appropriate treatment option. Currently, there are only case series that show some pruning of the vasculature with long-term bevacizumab, but this is not a contraindication for SIRT if bevacizumab is stopped at least 6 weeks prior to the procedure, even though all ongoing Phase III study protocols are administering bevacizumab only after SIRT.

**Conclusion**
These case histories illustrate the value of a multidisciplinary team approach for the optimal management of patients with mCRC, considering not only treatment efficacy, but also the impact of chemotherapy with or without biologicals on HRQoL in the palliative setting.

In conclusion, SIRT is an important treatment option for patients with liver-only and liver-dominant mCRC that should be considered during several lines of therapy. Further data from well-designed randomized controlled trials are eagerly anticipated in order to define exactly how SIRT should be integrated into routine clinical practice.

**Financial & competing interests disclosure**
RA Sharma receives research funding from the Bobby Moore Fund of Cancer Research UK, the Medical Research Council, Sirtex Medical Ltd, the CRUK Experimental Cancer Medicines Centre Oxford and the NIHR Biomedical Research Centre Oxford. M Peeters and J Taïeb have received research funding and honoraria from Sirtex Medical Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.
References


17. FOLFOX Plus SIR-Spheres Microspheres Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer (SIRFLOX) (NCT00724503). www.sirfox.com

18. Roswell Park Cancer Institute. (FOXFIRE Global STX0112) Assessment of Overall Survival of FOLFOX6m Plus SIR-Spheres Microspheres Versus FOLFOX6m Alone as First-Line Treatment in Patients with Non-Resectable Liver Metastases from Primary Colorectal Carcinoma in a Randomized Clinical Study (NCT01721954). www.roswellpark.org/clinical-trials/list/2378


Colorectal Cancer provides a concise, readable overview of current and future management options in a fast-moving field, ideal for the busy clinician or healthcare professional.

Email us to set up your FREE 30-DAY TRIAL

_trials@futuremedicine.com_

Citations:
EMBASE/Excerpta Medica

www.futuremedicine.com
The evidence for resection post-selective internal radiation therapy

Benjamin Garlipp*1 & Christiane J Bruns1

Selective internal radiation therapy (SIRT) has become a well-established modality for the palliative treatment of primary and metastatic liver tumors. As a consequence of the growing experience with this treatment, research has recently focused on its potential as a component in the management of patients for curative treatment. However, reports on the use of surgical resection, local tumor ablation or liver transplantation in conjunction with SIRT have hitherto been limited to individual case studies and small case series (usually comprising fewer than five patients), making it difficult to define the future role for SIRT in this setting.

The rationale for using SIRT in conjunction with surgery aiming for cure in patients whose disease appears to be beyond resectability comes from the observation that SIRT yields very high objective response rates. In mCRC, the objective response rate to chemotherapy has been demonstrated to be a valid surrogate for the secondary resection rate of primarily unresectable liver metastases [16]. Response rates of up to 91% have been demonstrated in treatment-naive patients treated with SIRT [8,17]. Even in chemotherapy-refractory patients receiving SIRT as a salvage treatment, response rates of up to 40% have been reported. In a recent study of 20 patients with mostly treatment-naive colorectal liver metastases who were treated with either folinic acid (leucovorin), fluorouracil, oxaliplatin chemotherapy regimen (FOLFOX) or folinic acid (leucovorin), fluorouracil, irinotecan (FOLFIRI) chemotherapy and received SIRT to one liver lobe only (thus using the contralateral lobe as the chemotherapy-only comparator), both anatomic and metabolic response rates (as measured by 18F-fluorodeoxyglucose PET) were substantially higher in the liver lobe receiving SIRT, providing evidence that SIRT may increase response rates compared with chemotherapy alone [18]. SIRT has also been compared with transarterial chemoembolization (TACE) as the standard treatment for nonresectable early- to intermediate-stage HCC, demonstrating a strong trend towards higher response rates in patients treated with SIRT [19]. Without the use of surrogates, however, it is difficult to assess how SIRT compares with other treatment modalities with respect to outcomes.

Keywords
• downstaging
• hepatocellular carcinoma
• liver metastases
• parenchymal hypertrophy
• selective internal radiation therapy
to achieving secondary resectability, because resectability or nonresectability always depends on individual judgment by a liver surgeon, taking into account personal experience as well as various patient-related factors. An attempt at providing objective data on changes in resectability has been made in the CELIM trial using a blinded panel of hepatobiliary surgeons who reviewed baseline and follow-up imaging studies of mCRC patients treated with cetuximab-based chemotherapy [20]. In order to more clearly define the capacity of SIRT to induce secondary resectability in mCRC, a retrospective analysis of patients treated with chemotherapy plus SIRT using a similar methodology is currently being developed at Magdeburg University, Germany (the REsect study).

### Induction of parenchymal hypertrophy

Following reports of ‘radiation lobectomy’ or ‘radiation segmentectomy’ (generally referring to the application of supratherapeutic, ablative activities of yttrium-90 (Y-90) to limited tumor-bearing areas of the liver, resulting in compensatory hypertrophy of the nontreated hepatic parenchyma), a marked interest in a possible use of this phenomenon in a surgical context has evolved in recent years. It has been demonstrated that contralateral liver hypertrophy also develops following unilobar application of regular therapeutic activities of Y-90 microspheres [21,22], implying the possible employment of SIRT as a means of contralateral hypertrophy induction in patients with unilobar tumor involvement who are candidates for surgery, but who are at risk of developing postoperative liver failure due to the small size of the future liver remnant. Although SIRT induces contralateral hypertrophy to a lesser extent than portal vein embolization [23], portal vein embolization may stimulate tumor growth along with hypertrophy induction. Patients with tumor lesions adjacent to vital vascular or biliary

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients (n)</th>
<th>Therapy</th>
<th>Context</th>
<th>Outcome of radical therapy (resection, transplantation, ablation)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al. (2001)</td>
<td>36</td>
<td>SIR-Spheres* + HAC</td>
<td>First</td>
<td>mCRC</td>
<td>1 resected</td>
</tr>
<tr>
<td>Sharma et al. (2007)</td>
<td>20</td>
<td>SIR-Spheres* + FOLFOX</td>
<td>First</td>
<td>mCRC</td>
<td>2 resected</td>
</tr>
<tr>
<td>Sangro et al. (2010)</td>
<td>23</td>
<td>SIR-Spheres*</td>
<td>Consolidation</td>
<td>mCRC</td>
<td>3 partial hepatectomy ± ablation (recurrence: 2 out of 3 in 6 months)</td>
</tr>
<tr>
<td>Chua et al. (2010)</td>
<td>1*</td>
<td>SIR-Spheres*</td>
<td>Consolidation</td>
<td>mCRC</td>
<td>1 resected</td>
</tr>
<tr>
<td>Lim et al. (2005)</td>
<td>30</td>
<td>SIR-Spheres* + 5-FU</td>
<td>Second–fourth</td>
<td>mCRC</td>
<td>1 resected</td>
</tr>
<tr>
<td>Cosimelli et al. (2010)</td>
<td>50</td>
<td>SIR-Spheres*</td>
<td>Salvage</td>
<td>mCRC</td>
<td>2 resected</td>
</tr>
<tr>
<td>Pini et al. (2010)</td>
<td>1*</td>
<td>SIR-Spheres* &gt; chemotherapy</td>
<td>Salvage</td>
<td>mCRC</td>
<td>1 resected</td>
</tr>
<tr>
<td>van den Eynde et al. (2008)</td>
<td>21</td>
<td>SIR-Spheres* + 5-FU</td>
<td>Salvage</td>
<td>mCRC</td>
<td>1 resected</td>
</tr>
<tr>
<td>Iñarrairaegui et al. (2012)</td>
<td>21</td>
<td>SIR-Spheres*</td>
<td>UNOS T3</td>
<td>HCC</td>
<td>3 resected and 2 transplantation; 1 ablated then resected</td>
</tr>
<tr>
<td>Pracht et al. (2013)</td>
<td>18</td>
<td>TheraSphere*</td>
<td>Lobar HCC + ipsilateral PVI</td>
<td>HCC</td>
<td>4 downsized for liver transplantation or surgical resection and 2 finally achieved radical therapy</td>
</tr>
<tr>
<td>Lau et al. (2004)</td>
<td>49</td>
<td>Chemoembolisation ± SIR-Spheres*</td>
<td>Unresectable BCLC stage A or B</td>
<td>HCC</td>
<td>28 resections</td>
</tr>
<tr>
<td>Tabone et al. (2013)</td>
<td>5</td>
<td>SIR-Spheres*</td>
<td>BCLC stage C with PVI</td>
<td>HCC</td>
<td>1 resected</td>
</tr>
</tbody>
</table>

*Yttrium-90 resin microspheres.
*Yttrium-90 glass microspheres.
5-FU: 5-fluorouracil; BCLC: Barcelona Clinic Liver Cancer; FOLFOX: Folinic acid (leucovorin), fluorouracil, oxaliplatin; HAC: Hepatic arterial chemotherapy; HCC: Hepatocellular carcinoma; mCRC: Metastatic colorectal cancer; PVI: Portal vein invasion; UNOS: United Network for Organ Sharing.
structures who are at risk of becoming unresectable if their tumor progresses may therefore be candidates for the preferential use of SIRT in order to induce contralateral hypertrophy and provide tumoricidal treatment at the same time. A prospective, randomized study protocol comparing secondary liver resection rates following portal vein embolization vs unilateral SIRT in patients requiring preoperative induction of contralateral liver hypertrophy (the Hypertrophy through RadioEmbolization to improve secondary ReSection rates — HypeREsect study) has been developed at Magdeburg University and patient recruitment is scheduled to start in 2015.

Safety of liver surgery following SIRT
The safety of liver surgery following SIRT is an issue that merits particular attention. While no major surgical complications directly attributable to preoperative SIRT have been reported, SIRT may induce histological changes that are consistent with sinusoidal obstruction syndrome, particularly in conjunction with chemotherapy [24]. Sinusoidal obstruction syndrome induced by oxaliplatin-based chemotherapy has been demonstrated to increase postoperative morbidity [25], and concomitant SIRT may theoretically potentiate this effect. However, the reported experience regarding the safety of surgery following SIRT has been encouraging so far, showing no increase in postoperative morbidity or mortality [26]. While no explicit data on the optimal timing of surgery after SIRT with regards to safety exist, an interval of at least 8 weeks should be observed in order to avoid the phase of acute radiation-induced parenchymal changes. A systematic work-up of the experience with surgery following SIRT focusing on safety end points is currently being performed within a global retrospective study (the P4S study). Data from the study are expected to be available by the end of 2014.

Ongoing studies
In summary, the efficacy signals for SIRT from palliative studies strongly suggest its potential for future use in potentially curative multidisciplinary treatment for primary and secondary liver cancer. In early- to intermediate-stage HCCs that are not primarily amenable to surgical or locally ablative treatment, the current treatment standard that SIRT needs to be compared with is TACE; however, the evidence for TACE in HCC mainly comes from two landmark randomized controlled trials in which a limited number of patients with large and multinodular tumor involvement was included [27,28]. Thus, there is a population of HCC patients for whom there is only limited evidence for TACE, providing a rationale for using SIRT as an upfront treatment in these patients. Prospective comparative efficacy data on SIRT versus TACE are expected in 2018 from a randomized Phase II trial (PREMIERE; NCT00956930). In mCRC, although high response rates suggest that SIRT may provide additional benefits compared with chemotherapy alone for downsizing tumors to resection, evidence is still pending as to whether it actually increases the cure rate in conjunction with surgery. This will depend on the outcome of the SIRFLOX and FOXFIRE randomized controlled trials [29,30], both of which are investigating the use of chemotherapy plus SIRT versus chemotherapy alone in the first-line treatment of mCRC. The data from both of these trials will be entered into a combined analysis together with data of 200–300 additional patients to form the FOXFIREGlobal study [31], which will provide a unique dataset of at least 1022 patients for the analysis of overall survival as its primary end point, with secondary end points including intra- and extra-hepatic progression-free survival, rate of secondary resection or local ablation and objective response rate.

Financial & competing interests disclosure
B Garlipp and CJ Bruns have received lecture fees from and have been on advisory boards for Sirtex Medical Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References
2 Lim L, Gibbs P, Yip D et al. A prospective evaluation of treatment with selective internal radiation therapy (SIR-Spheres) in patients with unresectable liver metastases from...
symposium paper  Garlipp & Bruns

7 Chua TC, Bester L, Akther J et al. Successful right hepatectomy after four treatments of yttrium-90 microspheres (SIR-Spheres) and concomitant FOLFOX as bridging therapy to resection of colorectal liver metastases. Ann Cancer Res. 30(7), 3005–3007 (2010).
29 FOXFIRE study website. www.octo-oxford.org.uk/alltrials/trials/FOXFIRE
30 SIRFLOX study website. www.sirflox.com
31 FOXFIREGlobal study website. http://foxfireglobal.sirtex.com

future science group
The safety of resection post-selective internal radiation therapy

Fernando Rotellar*, Fernando Pardo & Patricia Martínez-Ortega

Over the past few years, selective internal radiation therapy (SIRT) using yttrium-90 microspheres has increasingly gained recognition for its utility in the management of hepatic tumors. Formerly considered exclusively as a palliative option for unresectable tumors, SIRT has now been shown to improve disease control and even downsize some tumors in small published case series. SIRT is also being considered as a tool for rescuing patients for surgery. As surgical resection remains the only curative option for secondary hepatic tumors and surgical resection (transplantation or ablation) for early-stage hepatocellular carcinoma (HCC; primary liver cancer), a renewed interest by surgeons in SIRT is emerging [1].

Before surgery

• Tumor downstage & contralateral hypertrophy
Resectability is determined not only by the free tumoral margin, but also by the need to preserve an adequate percentage of remnant liver volume. It is well known that the regenerative capacity of the liver enables ambitious major resections, such that a remnant of approximately 25–30% of a healthy liver is considered adequate. This remnant needs to be increased to 40% in cirrhotic livers or after high doses of chemotherapy. Alternatively, in cases where the liver remnant is scarce, portal vein embolization is commonly used in order to induce contralateral hypertrophy, but this requires an additional procedure. Associating liver partition and portal vein ligation for staged hepatectomy (the ALPPS technique) has recently been used by some groups in order to induce hypertrophy of the remnant liver. Nevertheless, the available evidence from the early ALPPS experience suggests that this technique is associated with high rates of morbidity and mortality and early tumor recurrence [2].

We have recently published data showing that, in our experience, most patients with initially unresectable HCC could be downstaged to radical therapies following initial treatment with SIRT [3]. This was made possible by an increase in the liver remnant induced by single-lobe SIRT [4]. Contralateral lobe hypertrophy is one of the most important features of SIRT compared with other transarterial treatments, including transarterial chemoembolization. This concept of radiation lobectomy, first proposed by Gulec et al. in 2009 [5], enables the simultaneous treatment of the hepatic disease in one lobe and the induction of hypertrophy in the contralateral lobe [1]. This capacity of SIRT for inducing hypertrophy of the untreated liver (and therefore reaching an adequate remnant volume after resection) helps to diminish the risk of liver failure following surgery.

• Timing of surgery
It is considered that an adequate interval between SIRT and liver resection should be approximately 8 weeks [6]. Moreover, a 6–12-week waiting period serves as a test of time that provides information

*HPB & Liver Transplant Unit, Department of General & Abdominal Surgery, University Clinic of Navarre, University of Navarre, Avda. Pío XII no. 36, Pamplona, Spain
*Author for correspondence: Tel: +34 948 296789; Fax: +34 948 296500; frotellar@unav.es

KEYWORDS
• liver tumors
• radioembolization
• selective internal radiation therapy • surgery
• yttrium-90
on the biology of the tumor(s), thereby better delineating those patients who are optimal candidates for resection. Although much research is still needed in order to predict the extension of segmental or lobar atrophy/hypertrophy after SIRT, this is certainly an appealing use of this procedure, not only in HCC, but also in selected patients with liver metastases [1].

Outcome of the surgical procedure

● Technical aspects: perilesional adhesions & the laparoscopic approach

At the Clínica Universidad de Navarra (Spain), we have radically treated 30 patients (either with liver transplant or with resection) after SIRT. We have not found any additional technical difficulties when performing liver surgery after SIRT except for a particular subgroup of patients with bulky tumors located in the infra-diaphragmatic or pericaval right lobe. In some cases, we have found dense firm adhesions to the diaphragm or the caval vein. Nevertheless, in our experience, these adhesions did not impede the satisfactory completion of the surgery, nor did they require any additional procedures in any case. We have identified only one published case in which perilesional adhesions were described after SIRT that necessitated a partial diaphragmatic resection [7].

SIRT treatment does not preclude a laparoscopic approach when technically feasible [8]. We have successfully operated on two cirrhotic patients using this minimally invasive approach after SIRT. In the first case, the patient had received SIRT treatment 8.5 months earlier, and a laparoscopic resection of an HCC in segment 6 was performed. In the second case, a patient with hepatitis C virus cirrhosis and two HCC nodes in the right lobe underwent a total laparoscopic right heptectomy at 2 months post-SIRT. In both cases, no intra- or post-operative transfusions were needed and the postoperative courses were uneventful. The patients were discharged on the third and fourth postoperative days, respectively. In the second case, SIRT not only treated the tumoral disease, but also increased the left lobe volume that was initially insufficient, thus enabling the safe performance of the right heptectomy.

● Morbidity & mortality & oncologic results

Again, the available evidence is scarce regarding morbidity and mortality and oncologic outcomes. Our experience (from the referred 30 cases; data not shown) and the published experiences of other centers [8,9] suggest that additional morbidity is minimal (if any) as a consequence of SIRT and comparable to liver resection after other neoadjuvant regimens. Nevertheless, future large case series and comparative studies are warranted.

The ongoing P4S study is an international retrospective analysis of more than 20 centers across Europe, the USA and the Asia–Pacific region. The aim of this study is to assess the peri-operative and postoperative morbidity/mortality associated with liver resection or transplantation following SIRT using SIR-Spheres® (Sirtex Medical Ltd, Sydney, Australia) in two cohorts

---

**Box 1. The P4S study.**

**Rationale**

- Low-level evidence regarding surgery post-SIRT
- As SIRT is increasingly used earlier in the treatment paradigm, data on the safety of post-SIRT liver surgery will be needed in order to guide treatment planning
- Recent EU and global surgical advisory boards recommended a global initiative to retrospectively collect data post-SIRT liver surgery for an analysis of safety

**Study design**

- International, multicenter, exploratory retrospective study of approximately 120 patients resected or transplanted up until January 2013
- Anonymized data to be collected retrospectively

**Primary end point**

- Ninety-day postoperative morbidity and mortality (assessed as Clavien–Dindo score ≥3)

**Secondary end points**

- Postoperative hospital stay
- Overall survival (from date of first SIRT and date of surgery)
- Timing of surgery relative to first SIRT treatment

SIRT: Selective internal radiation therapy.
of patients with either primary tumors (HCC and/or cholangiocarcinoma) or liver metastases from any primary tumor.

With regards to tumoral recurrence, and as suggested by Berry [6], there seems to be no reason as to why the results with this technique should not be similar to those obtained after other neoadjuvant treatments. However, further observational studies are necessary in order to precisely define the long-term oncological outcomes of these patients.

Conclusion
SIRT has demonstrated an exceptional capacity for controlling primary or metastatic liver tumors and even increasing the contralateral untreated lobe. As a consequence, several authors have reported conversions to radical surgery in previously unresectable tumors. Future studies will provide evidence on the surgical and oncological outcomes of this group of patients who were rescued following SIRT for potentially curative surgery.

Financial & competing interests disclosure
F Rotellar and F Pardo have received honoraria and travel assistance from Sirtex Medical Ltd for presentations and/or participation in medical symposia and the European advisory board. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References
7 Chua TC, Bestor L, Akther J et al. Successful right hepatectomy after four treatments of yttrium-90 microspheres (SIR-Spheres) and concomitant FOLFOX as bridging therapy to resection of colorectal liver metastases. Anticancer Res. 30(7), 3005–3007 (2010).
Toward best practice in the diagnosis and treatment of melanoma

Melanoma Management

Be one of the first to contribute to this exciting new journal

Ensure your work is seen by readers all over the world

Submit your paper quoting ‘MMTOA’ and receive free open access for your paper for the first month following publication

www.futuremedicine.com
Liver function considerations for post-selective internal radiation therapy resection (hepatocellular carcinoma and metastatic colorectal cancer)

Bruno Sangro*

Besides isolated changes in liver function tests, a form of sinusoidal obstruction syndrome appearing 4–8 weeks after selective internal radiation therapy (SIRT; also known as radioembolization) as jaundice, mild ascites and a moderate increase in γ-glutamyl transpeptidase and alkaline phosphatase has been described in noncirrhotic patients as radioembolization-induced liver disease (REILD) [1]. A similar syndrome may appear within the same time frame in cirrhotic patients with hepatocellular carcinoma, although the spontaneous liver decompensation that occurs in cirrhotics is impossible to differentiate from REILD [2].

REILD seems to develop only in patients with cirrhosis or in noncirrhotic patients exposed to systemic chemotherapy prior to SIRT [1]. In the largest series published on this topic, the incidence rates of all-grade and severe REILD were 5.4 and 2.2%, respectively [3]. Factors that may impact on the occurrence of REILD include: the dose of radiation delivered and the volume of liver tissue involved [4]; prior liver function and functional reserve (e.g., as measured by total bilirubin or potentially by indocyanine green retention rate at 15 min clearance [5,6]); and prior or concurrent use of other antineoplastic therapies [7]. In the surgical setting, there are a number of well-recognized clinical risk factors that are associated with a low functional liver reserve compared with remnant liver volume (so-called ‘small-for-size syndrome’), such as age, steatosis, steatohepatitis, hepatitis, fibrosis and cirrhosis, as well as intraoperative blood loss and ischemia, obstructive cholestasis and preoperative chemotherapy [8,9]. However, the concurrent use of SIRT in combination with either oxaliplatin with fluorouracil and folinic acid (FOLFOX) or irinotecan as first- and second-line therapies, respectively, has produced little liver toxicity in patients with liver metastasis from colorectal cancer [10,11], so the impact on resectability relies mainly on the impact of subclinical radiation-induced liver damage on the liver functional reserve (similar to what occurs with oxaliplatin-containing regimes [12,13]).

Besides a potential effect of liver-protecting agents, such as ursodeoxycholic acid, the prevention of liver damage mainly relies on treatment design and dosimetry [3]. However, the absence of a clear dose–response relationship between the activity prescribed and the appearance of REILD [14] argues against the use of purely dosimetric approaches to the activity calculation, in which the activity only depends on the estimated dose of radiation delivered to the tumor and nontumoral tissues and not on the volume, status and function of the targeted liver.

**Modified protocol for SIRT**

We have recently proposed a modified protocol for the activity calculation of yttrium-90 resin microspheres so that with whole-liver treatment, for example, a 10–20% reduction in the calculated activity was applied on a general basis, which could be further reduced (towards 0.8 GBq/l) for those patients with cirrhosis or those heavily exposed to prior chemotherapy who had a small tumor burden or a reduced liver volume [3]. For selective treatment, the partition model was used in two...
**Factors determining the safety of resection post-SIRT**

Poor liver function and portal hypertension determine the likelihood of postoperative complications after partial hepatectomy. When estimated by indocyanine green clearance, a poor liver functional reserve also correlates with postoperative complications. Unfortunately, there are virtually no data on the effect of SIRT on liver functional reserve. Hence, close evaluation of liver function by clinical data (ascites and hypersplenism) or laboratory parameters (increased bilirubin, reduced albumin and prolonged international normalized ratio) is mandatory when considering liver resection in a patient treated by SIRT. Overall, the best way to ensure safe post-SIRT resection is to minimize the impact of SIRT on the liver functional reserve by preserving as much liver volume as possible, adapting the prescribed dose to the patient characteristics and designing SIRT with the potential rescue resection in mind.

**Financial & competing interests disclosure**

B Sangro has received lecture and consulting fees from Sirtex Medical Ltd and Bayer Healthcare. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.
Liver function considerations for post-selective internal radiation therapy resection  

SYMPOSIUM PAPER

References


Hepatic Oncology

Your dedicated resource for hepatic cancer management

NEW JOURNAL 2014

SUBMIT YOUR PAPER

Be one of the first to contribute to this exciting new journal

Ensure your work is seen by readers all over the world

Submit your paper to: info@futuremedicine.com

ISSN: 2045-0923
Volume: Number 1
Frequency: 6 issues per year
Bridging and downstaging to transplantation in hepatocellular carcinoma

Giuseppe Maria Ettorre*,1, Giovanni Battista Levi Sandri1, R Santoro1, Pasquale Lepiane1, Marco Colasanti1 & Giovanni Vennarecci1

Bridging treatment is used to manage patients while on the waiting list for liver transplantation in order to control hepatocellular carcinoma (HCC) to within the Milan criteria (i.e., a single nodule of up to 5 cm or multiple small nodules of ≤3 cm without vascular invasion). Alternatively, for patients either going onto the transplant waiting list or while on the waiting list, downstaging can be considered in order to reduce the size, number and eventually HCC macrovascular invasion to within the Milan criteria.

The Milan criteria offer patients optimal survival over 5 years (87%) [1]. A recent meta-analysis by Mazzaferro and colleagues of 19 studies in more than 3900 patients confirmed that patients with chronic hepatitis and cirrhosis and HCC within the Milan criteria achieved similar post-transplant survival rates to those with non-HCC indications [2]. Despite a number of proposed extensions to the Milan criteria in order to capture patients who may achieve a similar outcome (including those with an increased number of tumours or size of tumours; Figure 1) [3], the Milan criteria remain the benchmark for the selection of HCC patients for liver transplantation [4,5]. Data from the USA suggest that patients outside the Milan criteria would need to achieve 5-year survival rates of 60% or higher in order to prevent a substantial reduction in the life-years available to the entire population of candidates for liver transplantation [4,6]. Clearly, as we move further away from the stringent criteria defined by the Milan group, the cost-effectiveness of transplantation diminishes, carrying a greater price to patients and the healthcare system [7].

Clinical experience with selective internal radiation therapy for downstaging

Recently, there has been a paradigm shift in the management of patients for liver transplantation from open resection to laparoscopic (robotic) liver resection [8,9]. At our center, we are also increasingly using selective internal radiation therapy (SIRT) with yttrium-90 microspheres for the downstaging of patients as an alternative to transarterial chemoembolization (TACE) and ablation [10]. This decision is based on data from a retrospective analysis of patients with HCC beyond the Milan criteria, in which Lewandowski et al. compared SIRT with TACE and showed that SIRT was a better tool than TACE for downstaging the disease to within transplant criteria (i.e., from United Network for Organ Sharing [UNOS] T3 to UNOS T2) [11]. For small nodules of less than 3 cm and those between 3 and 5 cm in diameter, SIRT achieved 100% necrosis in 89% and 59% of cases in explanted livers, respectively, demonstrating a strong correlation between radiologic and pathological findings [12].

Currently, SIRT is mainly used in the palliative setting in patients with either Barcelona Clinic Liver Cancer stage B or C HCC [13]. Within this setting, a recent study has proposed a model for predicting the prognosis of patients following SIRT [14]. However, data from Iñarrairaegui et al. of the Pamplona group have demonstrated that a few patients who receive SIRT with palliative


© 2014 Future Medicine Ltd

Future Oncology

1 General Surgery & Transplantation Unit, San Camillo-Forlanini Hospital, Circonvallazione Gianicolense 87, 00152 Rome, Italy
*Author for correspondence: Tel.: +39 06 5870 4816; Fax: +39 06 5870 4441; gmettorre@scamilloforlanini.rm.it

KEYWORDS
• downstaging
• hepatocellular carcinoma
• liver transplantation
• selective internal radiation therapy • yttrium-90 radioembolization
intend are downstaged for radical treatment [15]. For these patients, SIRT affords a significantly improved overall survival (median 41.5 months since radical therapy) compared with those of the same stage (UNOS T3) who received palliative treatment only and who were not eligible for radical treatment after SIRT (median survival: 22.0 months; 95% CI: 15.0–30.9). In a similar study, investigators from San Camillo Hospital (Italy) have also demonstrated the utility of SIRT in 26 HCC patients who were either downstaged (n = 21) or bridged to liver transplantation (n = 5), and of these patients, ten and four from each group, respectively, have received a liver transplantation [16]. We found that the model for end-stage liver disease (MELD) score remained stable in all except one of these patients over the 6 months while they were on the transplant list, and after 26 months of follow-up, only two patients had died following transplantation in this case series. We are also pleased to report that a published case from our group demonstrates that a patient with portal vein invasion who was successfully downstaged and received a liver transplant 20 months

Table 1. Clinical practice considerations for selective internal radiation therapy in the context of liver transplantation.

<table>
<thead>
<tr>
<th>Role</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional radiologists</td>
<td>Evaluate each candidate for SIRT with a view to transplantation, working in close collaboration with the surgeon. Avoid damage to the vascular endothelium. Shorten the interval between staff decision and SIRT. Embolize the HCC as distally as possible. Embolize the gastroduodenal artery and right gastric artery far from the ostium.</td>
</tr>
<tr>
<td>Hepatologists/oncologists</td>
<td>For patients on the liver transplantation waiting list: Consider more strict surveillance. Consider whether SIRT could increase the MELD score. Consider the risk of radioembolization (SIRT)-induced liver disease. Control tumor status on the waiting list with regards to: number, size, vascular invasion and extrahepatic localization.</td>
</tr>
<tr>
<td>Nuclear medicine doctors</td>
<td>For patients on the liver transplantation waiting list: Shorten the interval between staff decision for the SIRT procedure in high-volume centers and consider avoidance of the first step for pulmonary shunts [18]. If possible, selective treatment is better. Consider a PET scan for the HCC evaluation.</td>
</tr>
<tr>
<td>Surgeons</td>
<td>The IVC preservation technique remains a feasible option. In the tumors located in the dorsal sector (segments 1–9) or posterior sector, consider the presence of strong adherence in the IVC dissection.</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; IVC: Inferior vena cava; MELD: Model for end-stage liver disease; SIRT: Selective internal radiation therapy.
after SIRT is still alive in 2014 (4 years after transplantation) [17].

**Conclusion**

SIRT does appear to have applications for the improved management of potential candidates for liver transplantation. Based on our experience, we have developed a series of clinical practice considerations for the multidisciplinary team in order to improve the outcomes in this group of patients (Table 1) [18].

**References**

Pain Management

SENIOR EDITORS | Martin Grabois, Professor and Chairman, Baylor College of Medicine, USA, Andrew SC Rice, Professor of Pain Research, Imperial College, London, UK

Pain Management covers key areas such as:

- Physiology and mechanisms of pain
- Transition from acute to chronic pain
- New concepts and breakthroughs in pain control
- Interventional procedures
- Non-pharmacologic approaches
- Acute and postoperative pain control
- Pain management in oncology
- Special pain syndromes
- Pediatric and aging health
- Pharmacology and addiction/abuse of pain medication
- Pharmacoeconomics and outcomes research

And much more...

“Now in its fourth volume, Pain Management continues to publish timely and comprehensive articles on a wide variety of topics. It is indeed a valuable resource to practitioners and academics alike.”

Andrew SC Rice, Professor of Pain Research, Imperial College London, UK

Free 30-day online personal trials are available, in order to claim your trial please email us at: trials@futuremedicine.com. Institutional trials are also available please contact us for further information.

www.futuremedicine.com/loi/pmt
Hypertrophy in the contralateral lobe post-selective internal radiation therapy

Derek M Manas*

In patients with unilateral, primary and secondary liver tumors potentially amenable to curative resection, the need to perform an extended hepatectomy in order to affect a cure can often be hampered by insufficient liver volume in the future liver remnant (FLR). Similarly, patients who have cirrhosis or chemotherapy-associated liver injury often require >30% FLR [1]. Since it was popularized by Makuuchi et al. in 1990, portal vein embolization (PVE) of the tumor-bearing liver has become the technique of choice for the induction of contralateral liver hypertrophy [2]. Unfortunately, this leaves the ipsilateral tumor(s) untreated, often allowing disease to progress. Lobar selective internal radiation therapy (SIRT; or radioembolization) using yttrium-90 (Y-90)-labeled microspheres not only treats the tumor in the embolized lobe, but it can also often result in a volume reduction of the ipsilateral tumor-bearing lobe and hypertrophy of the contralateral lobe, thus increasing the chance of a successful liver resection.

SIRT is most commonly used as a palliative treatment, but it can also be performed in some instances in order to downstage patients to salvage surgery and to avoid disease progression for patients awaiting resection [3,4]. Some authors are now reporting hypertrophy in the spared hemiliver after lobar, segmental or sequential lobar SIRT [5,6], thereby raising the question of whether this procedure could be deliberately used in a manner similar to PVE.

Evidence for hypertrophy in the contralateral lobe post-SIRT (see Table 1)

Garlipp et al. performed a matched-pair analysis in order to compare the capacity for hypertrophy induction following treatment to the right hemiliver using either PVE or SIRT in patients with right-sided lobar metastases [7]. In total, 141 patients were treated by PVE and 35 received SIRT at two centers. Patients were matched for criteria that are known to influence liver regeneration following PVE. Twenty-six pairs were identified for assessment, with the primary end point being the relative change in FLR volume from baseline at follow-up. Although both modalities induced significant contralateral hypertrophy, PVE appeared to induce more significant contralateral lobe hypertrophy. However, SIRT was more effective in minimizing the risk of tumor progression in the treated lobe and had more of an effect on total liver volume (TLV), making it a more suitable modality for selected patients with substantial unilateral disease burden. More recently, Seidensticker et al. showed that, in 32 patients with right-sided tumors, right hepatic SIRT achieved superior contralateral liver hypertrophy compared with PVE, while simultaneously treating the ipsilateral tumors during the interval from treatment to liver surgery, thereby reducing the risk of tumor progression [8].

These findings have been further substantiated by Fernández-Ros et al., who reviewed 83 patients treated with unilobar SIRT [9]. More than half of the patients had cirrhosis with hepatocellular carcinoma. The main finding was of a progressive increase in the volume of the spared hemiliver (mean
The percentage of patients in whom the baseline ratio of spared volume to TLV was <40% fell from 56.6% at baseline to 29.4% at 10–26 weeks (p < 0.001). Although a significant increase in spleen volume was recorded, this was not associated with an increase in portal vein diameter. The mean ± standard deviation absolute decrease in the treated hemiliver was 321.9 ± 375.6 ml at >26 weeks (p < 0.001). These results remained significant when patients with disease progression were excluded from the analysis. Similar results were found irrespective of whether the left or right hemiliver was treated. Globally, the TLV (mean ± standard deviation) did not change significantly from baseline because the hyper trophy of the spared hemiliver compensated for the atrophy of the treated hemiliver.

In order to study more specific volume changes, Ahmadzadehfar et al. administered SIRT to 24 patients with liver metastases [10]. Seventeen of these patients had metastases in both liver lobes and seven had metastases only in the right lobe. The patients with bilobar disease underwent sequential treatment, starting with the right liver lobe. The median administered dose was 1.75 GBq. For the whole group, SIRT was associated with a median increase in the volume of the left liver of 34% (p = 0.001) and a median decrease in the volume of the right liver of 11% (p = 0.03). The volume of the spleen showed a median increase of 17% (p = 0.01). Analysis of the two groups separately showed median increases in the volume of the left lobe of 30% (p = 0.001) in the bilobar group and 70% (p = 0.01) in the unilobar group. There was no correlation between the injected dose and the volume alteration.

Vouche et al. demonstrated that the effect of SIRT is time dependent in an analysis of 83 patients with right unilobar disease, including 67 hepatocellular carcinomas, eight cholangiocarcinomas and eight colorectal cancers [11]. The TLV, tumor volumes, FLR and percentage of FLR hypertrophy were assessed pre- and post-treatment (using computed tomography/MRI). Significant changes in right lobe atrophy (p = 0.003), left lobe hypertrophy (p < 0.001) and FLR hypertrophy (p < 0.001) were observed at 1 month after SIRT and this was consistent at all follow-up time points. The median percentage of FLR hypertrophy reached 45% (range: 5–186%) after 9 months (p < 0.001) and the median maximal percentage of FLR hypertrophy was 26% (range: 14–86%). Five patients underwent successful right lobectomy.

### Conclusion

Numerous case series and cohort analyses have suggested that SIRT using Y-90-labeled microspheres is a safe and effective technique for the achievement of hypertrophy of the FLR. Although volumetric changes appear comparable (although slightly slower) with PVE, the synchronous treatment of the ipsilateral lobe tumor with SIRT is an added advantage. This technique may become a valuable bridge to curative resection.

### Financial & competing interests disclosure

DM Manas has received honoraria from Sirtex Medical for his participation in advisory boards. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.
Hypertrophy in the contralateral lobe post-selective internal radiation therapy

**References**


In-depth coverage includes:

- Themed sections divide review coverage into therapeutic area and disease state
- Biomarkers in drug discovery and development
- Optimum biomarker selection, validation and application
- Pharmacokinetic/pharmacodynamic modeling and simulation to improve and refine drug development
- Biomarker application, using pharmacoepidemiology, pharmacogenetics, pharmacogenomics and functional proteomic techniques
- Biomarkers for clinical safety assessment and predicting adverse effects
- Bioanalytical method development and validation
- Impact of biomarkers on medicine including regulatory and ethical issues

"Biomarkers in Medicine provides an important forum for reporting innovation, offering perspectives, and commenting on developments in the rapidly evolving field of biomarker research. As such, it is a key element of the framework upon which to build this nascent discipline."

Scott A Waldman, Thomas Jefferson University, USA

Free trials available
trials@futuremedicine.com
SYMPOSIUM PAPER

Latest selective internal radiation therapy recommendations from EU proctors

Geert Maleux*

The Training, Evaluation & Certification program

Proctors are suitably qualified physicians or clinicians, mostly interventional radiologists with extensive experience in selective internal radiation therapy (SIRT) using yttrium-90 (Y-90) resin microspheres (SIR-Spheres® microspheres; Sirtex Medical Ltd, Australia), who have been contracted to act as trainers on behalf of Sirtex.

The Training, Evaluation and Certification program is consistent with the US Nuclear Regulatory Commission (NRC) guidelines that require a new authorized user to attend three training sessions delivered by either a Sirtex representative or trained physician proctor. After three procedures, the proctor reviews the center’s procedures in order to confirm that SIRT is being safely and effectively delivered since the outcome for patients is almost wholly determined by the skill of the interventional radiologist in performing this procedure.

For the first SIRT procedure, the institute is required to send pretreatment patient data to the proctor at least 5 days before the treatment date, including the patient’s history on prior chemotherapy/biological therapy, prior abdominal surgery, functional status and physical examination data (blood test results, imaging results, mapping arteriograms, technetium-99m macroaggregated albumin [99mTc-MAA] lung shunt study results and intended treatment plan). In accordance with established guidelines from the peer-reviewed medical literature, it is important that the interventional radiologist who performs the SIRT procedure also performs the baseline mapping angiogram, thereby ensuring continuity of patient care and better training.

Recommended procedures for generating mapping angiograms

When computed tomography (CT) angiography is available, it should be reviewed prior to undertaking the mapping angiography in order to assist in detecting anatomy and the need for selective angiography (including the superior mesenteric artery and celiac axis) [1]. The mapping procedures should be conducted using an automated pump injection in order to identify not only the right and left hepatic arteries, but also the gastric arteries and any other accessory vessels, which may need to be coil embolized in order to ensure the safe administration of Y-90 resin microspheres. Suggested arterial contrast injection rates and volumes (Table 1) should be individualized according to the patient and vessel caliber, with filming carried out into the late venous phase. When injecting approximately 4 mCi of 99mTc-MAA, the catheter tip must be positioned in the same place as intended for the injection of the Y-90 resin microspheres. Within 1 h of the 99mTc-MAA injection, planar scintigraphic imaging should be performed with regions of interest drawn around the lungs and the liver and the counts for each region measured [2]. Early scintigraphic imaging is essential for ensuring the accurate assessment of lung shunting (since shunt fractions that could result in >25-Gy lung radiation doses may exclude the patient from SIRT treatment). Importantly, the 99mTc-MAA study should be performed

Keywords

- delivery technique
- dosimetry
- periprocedural care
- selective internal radiation therapy

*Department of Radiology, University Hospitals Leuven, Herestraat 49, B3000 Leuven, Belgium; Tel.: +32 16 34 37 82; geert.maleux@uzleuven.be
within 4 weeks prior to the planned SIRT treatment date and generally not on the same day as the SIRT procedure. Combining Y-90 resin microspheres and ⁹⁹ᵐTc-MAA may, however, be feasible in appropriately selected patients. For example, investigators from University Hospital Bonn (Germany) combined Y-90 resin microspheres with a simultaneous second test angiogram of another lobe or segments in the same session in six patients [3]. In this study, immediate post-therapeutic ⁹⁹ᵐTc-MAA SPECT/CT showed only the distribution of ⁹⁹ᵐTc-MAA without any detectable Y-90-Bremsstrahlung SPECT/CT, while a post-therapeutic Bremsstrahlung SPECT/CT scan conducted 48 h later could be performed without any ⁹⁹ᵐTc-MAA contamination.

It is clear from the experience of the nuclear medicine physicians from University Hospital Bonn that SPECT/CT has much higher sensitivity and specificity than planar or nonattenuation-corrected SPECT for the assessment of extrahepatic MAA deposition [4]. In pre-SIRT planning, ⁹⁹ᵐTc-MAA SPECT/CT is the most valuable technique for identifying extrahepatic visceral sites at risk of post-SIRT complications. In these patients, further coil embolization may be necessary; alternatively, the catheter can be placed distally to the extrahepatic artery in order to ensure the safe delivery of SIRT (Figure 1). For the cystic arteries, however, coil embolization is not considered necessary because the respective risks of ischemic injury or radiation injury to the gallbladder are similar with and without embolization (~5%).

**Predictive value of intratumoral ⁹⁹ᵐTc-MAA uptake**

The response to SIRT was found to be independent of the degree of ⁹⁹ᵐTc-MAA uptake [5]. Therefore, it is the view of the proctors that SIRT should not be withheld from patients with colorectal liver metastases lacking intratumoral ⁹⁹ᵐTc-MAA accumulation.

**Dosimetry**

The calculation of the activity to be delivered should be discussed by the radiologist and the nuclear medicine physician during the multidisciplinary team meeting. Some important practice points to consider are as follows:

- The point of injection (tip of the catheter position) and the activity delivered must be marked on the scans for follow-up;
- The body surface area model is the preferred method of calculation of the prescribed activity;
- Tumor volume should be calculated (not estimated) from CT;
- Consider reduction in prescribed activity by 20–30% for the following patients:
  - Heavily pretreated;
  - Cirrhotics;
  - 5–10% tumor burden (high tumor burden; case dependent);
  - Small livers (<1200–1500 cc) [6].

These recommendations are based on a recent study from the Pamplona group, who showed that the incidence of radioembolization (i.e., SIRT)-induced liver disease was reduced by lowering the treatment intensity in patients who had received prior exposure to cancer chemotherapy, cirrhosis or a reduced liver and/or tumor volume [6]. By contrast, treatment intensity could be safely increased with more selective SIRT with a radical intent. In all patients, 600 mg/day of ursodeoxicolic acid was administered for 2 months post-SIRT [6].

**Periprocedural care**

The following recommendations have been published regarding periprocedural care [7]:

<table>
<thead>
<tr>
<th>Table 1. Suggested arterial rates and volumes recommended for generating mapping angiograms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel</td>
</tr>
<tr>
<td>Celiac axis</td>
</tr>
<tr>
<td>Proper HA</td>
</tr>
<tr>
<td>Replaced HA</td>
</tr>
<tr>
<td>Right or left HA</td>
</tr>
</tbody>
</table>

fps: Frames per second; HA: Hepatic artery.
Data taken from [1].
Figure 1. Procedure for identifying extrahepatic visceral sites at risk of post-selective internal radiation therapy complications.
SIRT: Selective internal radiation therapy; Tc-MAA: Technetium-macroaggregated albumin.

- Proton pump inhibitors must be given for at least 1 week after SIRT:
  - It would be better to start proton pump inhibitors therapy 1 week before SIRT, continuing for 4 weeks after SIRT.
- Pain medication should be given either before or during the SIRT procedure.
- Corticosteroids may be given 24 h before and for a minimum of 1 week after the treatment:
  - It would be better to administer 8 mg of corticosteroids every day for 4 weeks and 4 mg every day for another 4 weeks.
- Antiemetics are usually commenced on the morning of the day of SIRT treatment.
- Antibiotics are not recommended unless the patient has had biliary surgery, prior stent implantation or a bile duct obstruction.
- Carcinoid crisis prophylaxis: a short-acting somatostatin analog should be considered for the prevention of carcinoid crisis.
- Ursodeoxycholic acid 300 mg twice daily should be administered for (4 to) 8 weeks.
  In addition, the administration of sodium perchlorate 300 mg at a minimum of 2–4 h before the application of $^{99m}$Tc-MAA is recommended.
in order to inhibit the Na-I-symporter protein in the gastric mucosa, thereby making it easier to discriminate between gastric/extrahepatic MAA and gastric accumulation of free pertechnetate [8].

**General principles for repeat SIRT**

The following general principles should be applied when considering repeat SIRT [7]:

- The time interval from first or most recent Y-90 treatment should be at least 12 weeks (taking into account the typical tumor response suggested by the Response Evaluation Criteria In Solid Tumors [RECIST] or WHO of between 10 and 14 weeks post-SIRT);

- A more selective treatment strategy should be considered so that segments of the liver can be spared radiation during subsequent treatment;

- Interval therapies since the last SIRT can impact on liver tolerance and may lead to either a reduced planned activity or the avoidance of a lobe or segment for retreatment;

- Trends in functional liver reserve parameters (alkaline phosphatase, glutamic oxaloacetic transaminase, glutamate-pyruvate transaminase, bilirubin and albumin) over past 3 months are helpful.

**The Coldwell ‘sandwich’ delivery technique**

Today, it is recommended that Y-90 resin microspheres are injected using the Coldwell ‘sandwich’ delivery technique, which involves putting the aliquot of Y-90 resin microspheres into the line first, followed by 1 ml of sterile water then 1–2 ml of contrast (full strength). While using fluoroscopy, the entire content should be pulsed through the microcatheter using a 20-ml syringe constantly so that the pulsing creates a turbulent flow for the more even delivery of the microspheres. Once the contrast is observed (indicating that the microspheres have been delivered), the pressure on the sterile water syringe can be increased in order to check the flow in the treated artery. The advantages of this technique are: the catheter tip is watched continuously so that it does not inadvertently move into another artery; the flow is seen at each injection and so there is no need to carry out a true arteriogram that wastes contrast and time; and finally, the delivery is safer, since the operator immediately knows when the flow slows down.

**Financial & competing interests disclosure**

G Maleux is a proctor for Sirtex Medical Ltd. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

---

**References**


Optimizing the use of PET with selective internal radiation therapy

Patrick Flamen*

PET coupled with computed tomography (CT) is indicated for the management of patients undergoing selective internal radiation therapy (SIRT), both as an aid to treatment planning as well as for post-SIRT dosimetry and the assessment of the metabolic response. PET-CT plays an important role in not only identifying the target tumor volume, but also for the prognostic stratification of patients and the exclusion of those with significant metabolic activity in extrahepatic lesions that cannot be controlled with radiotherapy and/or systemic chemotherapy.

**18F-fluorodeoxyglucose PET-CT response to SIRT**

The use of structural/morphology-based imaging with CT/MRI has a very low accuracy for detecting responses to SIRT. Its use is mainly limited to the detection of progressive disease post-SIRT. 18F-fluorodeoxyglucose (FDG) PET-CT can be conducted in order to measure the metabolic response to SIRT at 6 weeks (recommended for the rapid identification of nonresponding lesions that might benefit from additional local treatment; e.g., radiofrequency ablation or external radiotherapy). A higher intensity of metabolic response is sometimes observed at 3 months; however, at this late time point, the PET response is very often counterbalanced by rapidly progressive lesions that were not present at the baseline PET or were located outside of the SIRT treatment field of view. SIRT responses, however, may be characterized by significant intraindividual heterogeneity with both the presence of responding and nonresponding lesions as measured by changes in the relative FDG uptake from baseline. For this reason, a 6-week FDG PET provides a valuable early indication of responses to SIRT. In a prospective trial, a significant correlation was shown between the probability of a response (as measured by the metabolic response with FDG PET at week 6 post-SIRT) and the intra-arterial perfusion of the tumor and simulated absorbed radiation dose (as measured using pretreatment technetium-99m-macroaggregated albumin [99mTc-MAA] SPECT-CT imaging) [1]. The selection of patients with hypervascularized lesions on 99mTc-MAA SPECT-CT significantly increases the predictive value of a treatment response and patient benefit. In cases of nonhypervascularized lesions on 99mTc-MAA SPECT-CT, the probability of a response is probably too low to justify SIRT. These findings were recently confirmed by Garin et al., who found a strong correlation between pretreatment 99mTc-MAA SPECT imaging in hypervascular hepatocellular carcinoma (HCC) lesions and the treatment outcome (either progression-free survival or overall survival) following SIRT [2].

**PET-CT for patient stratification**

FDG PET-CT is the most sensitive whole-body staging technique in most cancers that generally show a high metabolic activity (e.g., colorectal cancer, cholangiocarcinoma and breast cancer). However, two tumor types that constitute a major segment of patients sent for SIRT

*Nuclear Medicine, Institut Jules Bordet, Université Libre de Bruxelles (ULB), rue Héger Bordet, 1, B-1000 Brussels, Belgium; Tel: +32 2 541 3240; Fax: +32 2 541 3224; patrick.flamen@bordet.be

**KEYWORDS**

- FDG PET-CT response
- patient stratification
- selective internal radiation therapy • treatment planning
– neuroendocrine tumors (NETs) and HCCs – are known to have variable FDG uptake, which is related to grade, differentiation and rate of progression.

The utility of $^{68}$Ga-octreotate PET-CT for the detection and staging of metastatic NETs (mNETs) is well described in low-grade and intermediate-grade tumors [3]. The radiotracer targets the somatostatin receptor that is typically expressed in well or moderately differentiated NETs. Recent data indicate that high metabolic activity in low-grade tumors, as indicated by high FDG PET uptake, exhibits excellent predictive value for early tumor progression in mNETs. Both FDG PET and somatostatin receptor scintigraphy correlate well with progression-free survival and overall survival, especially for histologically confirmed low-grade mNETs [4]. In HCC, the extent of FDG uptake increases over time as the HCC lesions become more poorly differentiated. High standardized uptake values and/or high tumor:nontumor standardized uptake value ratios as measured by FDG PET in poorly differentiated HCC lesions [5] were found to be highly predictive of poor survival following orthotopic liver transplantation [6], as well as following locoregional chemoradiation therapy in locally advanced HCC [7]. In the future, this prognostic stratification of patients with mNETs and HCCs using FDG PET is likely to become an increasingly important approach for selecting the best candidates for SIRT and thereby improving the cost-effectiveness of this procedure. Practically, in our institution, all metastatic NET patients undergo a FDG PET-CT and a $^{68}$Ga-octreotate PET-CT. In patients with progressive (FDG-positive) liver metastasis and extrahepatic disease without FDG uptake (and no other signs of clinical progression), SIRT is the preferred method because FDG PET-CT indicates that the prognosis will mostly depend on the liver disease.

**FDG PET-CT for SIRT treatment planning**

Increasingly, centers are adopting a superselective approach for SIRT, which enables high doses of yttrium-90 (Y-90) to be delivered to discrete tumor-bearing regions of the liver. This requires careful pretreatment planning using integrated multimodality imaging (3D volume-rendering angio-CT fused with FDG and/or $^{68}$Ga-octreotate PET-CT) in order to develop a detailed picture of the vascular anatomy and the feeding artery/arteries of the tumor. With this mapping performed before the simulation arteriography, the interventional radiologist and nuclear medicine physician can determine the optimum catheter position for pretreatment simulation with $^{99m}$Tc-MAA.

**Y-90 PET-CT for SIRT treatment verification**

As shown in Figure 1, with the appropriate selection of patients (and tumors) for SIRT, a good correlation can be found with the pretreatment $^{99m}$Tc-MAA SPECT, the Y-90 PET-CT shortly after SIRT and the subsequent response as measured by FDG PET at week 6. Y-90 PET-CT techniques, which were first published by Lhommel et al., provide a high-resolution image of the biodistribution of Y-90 after SIRT from which the delivered dose of Y-90 can be calculated [8]. However, the disadvantage of this approach is that the image can take up to 60 min to develop, even with a Y-90 time-of-flight PET scan; nevertheless, this remains a very elegant approach for the evaluation of the actual distribution of the Y-90 microspheres after SIRT.

The QUEST study, sponsored by Sirtex Medical Ltd (Australia), aims to evaluate the reproducibility and determine the activity required in order to achieve measurable outcomes using a standard protocol across a range of PET scanners. Of interest are the clinically
relevant activity and imaging times, so that a correlation can be made between the calculated delivered dose and the response.

**Conclusion**

PET-CT has a central role in the management of patients with SIRT, both for patient selection (as a companion diagnostic tool if combined with predictive dosimetry obtained during simulation $^{99m}$Tc-MAA SPECT-CT) and for treatment planning of superselective SIRT. PET-CT may also facilitate post-SIRT dosimetry in the future (ongoing research), as well as post-SIRT response assessment, particularly for the early identification of nonresponding lesions.

**Financial & competing interests disclosure**

P Flamen has received research grants as well as honoraria for lectures from Sirtex Medical Ltd. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

**References**


CALL FOR PAPERS

The International Journal of Hematologic Oncology welcomes contributions on all aspects of hematologic oncology research, from epidemiology and pathology of the disease types to prospects for new treatments such as stem cell therapy and immunotherapy, and the diagnosis and management of hematologic cancers.

Ensure your work is seen by readers all over the world

Submit your paper quoting ‘IJHOA’ and receive free open access for your paper for the first month following publication

“International Journal of Hematologic Oncology is an exciting resource for clinicians and researchers alike, with comprehensive and timely coverage of topics within the field.”

– S Molica, Editorial Board Member, General Hospital “Pugliese-Ciaccio” Italy

ISSN: 2045-1393
Volume: Number 3 (2014)
Frequency: 6 issues per year
Citations: Chemical Abstracts

www.futuremedicine.com
SYMPOSIUM PAPER

Selective internal radiation therapy dosimetry

Andrew Kennedy*

Dosimetry is the calculation of radiation energy absorbed by tissue (measured in Grays [Gy]) as a result of exposure to indirect and direct ionizing radiation. The strength of a radioactive source is called its activity, which is defined as the rate at which the isotope decays over time. The concentration of radioactivity, or the relationship between the mass of the radioactive material and the activity, is called the specific activity. Specific activity is expressed as the number of curies or becquerels (Bq) per unit mass or volume. The higher the specific activity of a material, the smaller the physical size that the source is likely to be.

For selective internal radiation therapy (SIRT), a predefined activity (measured in GBq) of yttrium-90 (Y-90) is prescribed and delivered to a prespecified volume of liver (either whole, lobe or segment). However, there is no direct way to measure the absorbed energy (or dose) delivered by the Y-90 microspheres to the tumor and non-tumor tissue during the SIRT procedure, except using techniques such as Y-90 PET–computed tomography. Consequently, a direct correlation between the absorbed dose and outcomes (i.e., radiological response and toxicity) cannot be made at most centers. For safety purposes, the biological effect of the radiation (expressed as a summation of the effects of the radiation on the tissue parts) is calculated in Sieverts (Sv). Currently, most centers calculate the percentage activity of Y-90 that will be absorbed into the lung, tumor(s) and normal liver parenchyma based on the intensity of the technetium-99m-labeled macroaggregated albumin cloud on SPECT during the pretreatment simulation. From this image, it is possible to estimate the isodoses within and around the tumor (Figure 1) [1].

**Radioembolization-induced liver disease**

The goal of SIRT is to achieve uniform coverage by Y-90 in the tumor tissue while minimizing its effects on nontarget tissue. Seminal work in hepatic radiotherapy by Lawrence and colleagues has shown that complication rates do not occur unless the threshold of liver damage exceeds the functional reserve [2]. This concept (also known as the parallel architect model) means that small portions of the liver can tolerate irradiation well above 35 Gy without significant complications, as long as sufficient normal liver is spared from high-dose radiation exposure. While the clinical features of radiation-induced liver disease (RILD) caused by external beam radiotherapy are well recognized, radioembolization-induced liver disease (REILD) has clinical features much more akin to the effects of veno-occlusive disease caused by chemoradiation (Table 1) [3,4]. Risk factors associated with REILD, as identified by Sangro and colleagues of the Pamplona group, include activity >0.8 GBq/l delivered to the target liver volume, prior chemotherapy, cirrhosis, small liver volume (<1.5 l) and total bilirubin >1.2 mg/dl [3,5]. The Pamplona group also found that the severity and frequency of REILD can be significantly reduced (from 13.3% to 2.2%; p < 0.0001) through modifications in the treatment design and activity calculation (Figure 2), and with the addition of a prophylactic regimen administered over 2 months post-SIRT (i.e., oral ursodeoxycholic acid 300 mg twice daily and methylprednisolone.)

*Radiation Oncology Research, Sarah Cannon Research Institute, 3322 West End Avenue, Suite 800 Nashville, TN 37203, USA; Tel.: +1 615 524 4200; Fax: +1 615 524 4700; andrew.kennedy@scresearch.net

**KEYWORDS**
- dosimetry
- radioembolization-induced liver disease
- selective internal radiation therapy

8 mg every day [month 1] then 4 mg every day [month 2]) [5]. As illustrated in Figure 2, for patients with risk factors for REILD who are receiving whole-liver SIRT, the modified protocol recommends that the activity delivered should be reduced to <0.8 GBq/l. For patients receiving selective administration of SIRT, no more than 40 Gy should be delivered to the nontumor compartment (as assessed by the partition model) if the quality of the liver is poor. If the quality of the liver is good, much higher doses (≥100 Gy) to the tumor compartment are permitted.

The findings from the Pamplona group [3,5] are consistent with the results from a further large-scale retrospective study of 515 consecutive patients with either primary or metastatic liver lesions who were treated with resin Y-90 radioembolization at 14 US and two European centers [6]. In this study, the incidence of REILD/RILD was 4% over the 90 days following SIRT. Of these cases of REILD/RILD, 75% were from a single center that used the empiric method for calculating activity (now not recommended) instead of the body surface area (BSA) method. Other risk factors for REILD/ RILD were identified as small liver volume, high administered activity of Y-90 and more than six cycles of prior chemotherapy [6].

**Calculating the administered activity of Y-90 resin microspheres**

- **BSA method**

There is a wealth of published evidence from >1300 patients supporting the safety and efficacy of the BSA method for calculating the administered activity of Y-90 [7–11]. The MORE study is the largest SIRT series that evaluated consecutive patients who received resin Y-90 radioembolization at 11 centers in the USA [7]. Using the BSA formula in order to calculate activity, patients (mean age: 61.5 years) received a median of two (range: none to six) lines of chemotherapy prior to SIRT. The median tumor:liver ratio and Y-90 activity administered at the first procedure were 15% and 1.17 GBq, respectively, with a total reported incidence of 1.2% for hepatitis and 0.5% for REILD [7].

However, we have observed that with the increasing use of VEGF inhibitors such as bevacizumab, which inhibit angiogenesis, there has been a steady decline in the recommended activity of Y-90 that can be safely delivered for SIRT. Reflecting recent discussions in the medical literature, some adaptation of the calculated activity from the BSA method has also been recommended in cases where the liver is small (<1.5 l) in a large person (thereby increasing the risk of overdosing and REILD, as described above) or where the liver is large (>3.0 l) in a small person (thereby increasing the risk of underdosing and tumor progression).

---

### Table 1. Comparison of the clinical features of radiation-induced liver disease and radioembolization-induced liver disease.

<table>
<thead>
<tr>
<th>Feature</th>
<th>RILD*</th>
<th>REILD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>Anicteric</td>
<td>Elevated (&gt;3 mg/dl)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Rapid weight gain</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Presentation</td>
<td>2–16 weeks</td>
<td>4–8 weeks</td>
</tr>
<tr>
<td>AST and ALT</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Elevated</td>
<td>Possible</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Mortality</td>
<td>10–20%</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

*See [4]; †See [3].

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; REILD: Radioembolization-induced liver disease; RILD: Radiation-induced liver disease.

---

**Figure 1.** Estimated pretreatment dose based on technetium-99m-labeled macroaggregated albumin SPECT. Reproduced with permission from [1].
Figure 2. Work-up of the activity calculation using the modified protocol.
NTC: Nontumor compartment; TC: Tumor compartment.
Reproduced with permission from [5].

- **Partition model**
  There is evidence that the partition model, when appropriately applied using medical internal radiation dose principles, is also an effective and well-tolerated method for calculating Y-90 activity [5,12,13]. In 2012, an activity calculation algorithm was published that recommended that this model should only be applied to patients with a discrete tumor (such as those observed in some patients with hepatocellular carcinoma) that can be localized from the uninvolved parenchyma (Figure 3) [14]. Thus, relatively few patients with metastatic disease in the liver will qualify for partition model planning because they generally present with diffuse lesions infiltrating the normal parenchyma. If the calculated dose in the liver compartment is between 50 and 70 Gy, the safety of the procedure has to be considered in the context of the patient’s medical history and risk factors for REILD. If risk factors (e.g., cirrhosis or significant prior chemotherapy) are present, then the treated volume should be decreased (using sequential lobar or the segmental treatment approach) with a possible reduction in the calculated activity of the administered Y-90 (Figure 3).

**Conclusion**

The primary consideration for the application of SIRT is safety, which can be achieved through the correct selection of patients and the proper technique. The risk associated with the chosen technique also has to be appropriate for the treatment intent (i.e., palliation or cure). Liver function trends prior to Y-90 should always be considered and the calculated activity should be adapted accordingly for each patient. Moreover, SIRT requires a multidisciplinary team approach (both pre- and post-procedure). Postprocedural follow-up is essential so that an adaptive style can be implemented based on the outcomes of a regular review and/or an audit process.

**Financial & competing interests disclosure**

A Kennedy has received research funding from Sirtex Medical Ltd. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.
Figure 3. Activity calculation algorithm incorporating acceptable absorbed doses for uninvolved parenchyma.

†Underlying liver damage including cirrhosis due to alcohol consumption, hepatitis B or hepatitis C viruses and/or functional compromise after exposure to systemic chemotherapy or biologic agents.

BSA: Body surface area; CT: Computed tomography; CTHA: CT hepatic angiography; HCC: Hepatocellular carcinoma; 99mTc MAA: Technetium-99m macroaggregated albumin.

Reproduced with permission from [14].

References
7 Kennedy A, Ball D, Cohen SEA. Safety and efficacy of resin 90Y-microspheres in 548 patients with colorectal liver metastases.
progressing on systemic chemotherapy.


Articles published include key areas such as:

- Cancer immunotherapy, including cancer vaccines and passive immunotherapeutic approaches
- Restorative immunotherapy for AIDS and other immunocompromised patients
- Suppressive immunotherapy for autoimmunity diseases and transplantation
- Drug delivery systems, drug combinations and drug–drug interactions
- Summaries evaluating newly approved immunotherapeutic agents
- Newly identified immune targets of drugs

“Immunotherapy provides a timely discussion of current topics related to the understanding of human immune biology and the resulting applications for the treatment of immune pathologies. A highly recommended read for healthcare professionals in the immunotherapy field.”

Francesco M Marincola, National Institute of Health, USA
Liver metastases from neuroendocrine tumors

Andrew Kennedy*

Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that arise from the hormone-producing cells of the body’s nervous and endocrine systems. They are most frequently found in the small intestine and lung/bronchus, reflecting the density of neuroendocrine cells in these tissues [1]. Each type of tumor has distinctive clinical, histochemical and secretory features depending upon the cell type from which the tumor is derived and its location.

Overall, the incidence of NETs is rising [2]. The annual incidence of gastrointestinal and lung NETs are estimated to be between 2.55 and 3.5 per 100,000 of the population (5.96 per 100,000 of the African–American population), while pancreatic islet cell NETs occur in approximately 0.13–0.3 per 100,000 [1].

Although many clinicians consider NETs to be mostly benign, these neoplasms can exhibit a malignant clinical course with the development of metastatic disease, which is a predictor of poor survival (Table 1) [3]. Without obvious signs or symptoms, the diagnosis of NETs is often delayed, with 20–30% of patients presenting with advanced disease [3], including many (particularly with gastroenteropancreatic NETs) which metastasize in the liver [4].

Surgery should be offered when NETs are resectable and there is curative intent (or when debulking offers palliation) to patients who are fit and have disease that is limited to the primary/regional lymph nodes and/or potentially resectable metastases in the liver. For patients who are not fit for surgery, the aim of treatment is to improve symptom control (i.e., paraneoplastic endocrine or carcinoid syndrome) in order to maintain optimal quality of life and, where possible, improve survival. Treatment choices for the palliation of nonresectable disease include somatostatin analogs, biotherapy, targeted radionuclide therapy and locoregional treatments for predominantly localized liver disease (e.g., ablation [radiofrequency or microwave ablation], selective internal radiation therapy [SIRT] or transarterial embolization [TAE]/transarterial chemoembolization [TACE]; Figure 1) [5,6,7].

Selective internal radiation therapy

The hallmark of metastatic NETs (mNETs) is the hypervascular arterialization of the liver metastases [8], which makes these tumors a particularly attractive target for intra-arterial therapies. However, SIRT utilizing much smaller microspheres (25–35 μm) than those required for TACE (100–700 μm) differs significantly in its mechanism of action. Whereas the primary mechanism of SIRT is radiation cell killing [9] at the neovascular rim of the growing tumor, the mechanism of action for TACE is almost exclusively via hypoxia-induced cell death.

**Advantages & disadvantages of SIRT in mNETs**

When considering the appropriateness of SIRT for the management of mNETs, it is important to remember that the extent of hepatic disease tends to be prognostic for survival. Moreover,
mNETs often present in young, otherwise healthy patients with noncirrhotic livers who have had minimal chemotherapy and often no prior surgery. However, the tumors in the liver may be diffuse and/or numerous. One of the key challenges in the management of mNETs in the liver is often the multifocal nature of the disease in the liver (Figure 2), which requires careful consideration of the functional liver reserve for the safe delivery of SIRT.

Currently, TACE/TAE is the established and recommended therapy, although the clear superiority of one transarterial technique over others has not been demonstrated through a randomized controlled trial [10]. Chemotherapy options have increased over the last few years, including newer treatments that remain to be evaluated in carefully controlled safety studies with SIRT. There is currently a lack of evidence on the impact of SIRT on overall survival [5].
Patient selection for SIRT still needs to be refined in patients with mNETs. In my opinion, SIRT is indicated for mNETs in the liver when: there is liver-dominant tumor burden; liver tumor growth exceeds the growth of extra-hepatic metastases; and SIRT may reduce the burden of tumor in the liver and thereby alleviate the symptoms associated with paraneoplastic syndrome, hepatic capsule stretching (pain) or biliary obstruction/portal vein compression.

**Toxicities with SIRT**

In the USA, more than 99% of cases are discharged the same day after SIRT. Potentially serious events include: radiation/radioembolization-induced liver disease: incidence 1% (range: 0–4%); gastrointestinal ulcer: incidence <2% (range: 0–20%); acute constitutional symptoms (typically fatigue): incidence 44% (94% NCI Common Terminology Criteria for Adverse Events [CTCAE] grade 0–2); gastrointestinal symptoms (including short-term exacerbation of paraneoplastic syndrome): incidence 30% (95% grade 0–2); and biochemical changes: incidence 19% (mostly asymptomatic) [11,12].

**Published consensus on the role of SIRT in mNETs**

A recent review of 37 studies comprising 1575 patients evaluating TACE, bland embolization and SIRT concluded that these therapies are safe and effective in the treatment of unresectable liver mNETs [13]. The conclusions of the recently published Working Group of Neuroendocrine Liver Metastases, in terms of the quality of data for SIRT, are outlined in Table 2 [5]. Based on this evidence, the Working Group of Neuroendocrine Liver Metastases concluded the following:

- Moderate-quality studies support the use of SIRT instead of TAE or TACE in the hepatic metastases of NET;
- The quality and strength of the available reports does not allow determination as to preferred choice of SIRT, TAE or TACE for the best imaging and symptomatic response or survival;
- SIRT may have advantages over TAE/TACE in terms of reduced side effects and fewer treatments in a significant percentage of patients;
- Based on current European Neuroendocrine Tumour Society consensus guidelines, SIRT can be substituted for TAE/TACE in patients with liver-only disease and with limited extrahepatic metastases (Figure 3).

Overall, the tumor response rate with SIRT is approximately 50% (based on Response Evaluation Criteria In Solid Tumors [RECIST])

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients (n)</th>
<th>Study type</th>
<th>National Cancer Institute (evidence and end points)</th>
<th>GRADE (evidence)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>King et al. (2008)</td>
<td>34</td>
<td>Phase II</td>
<td>2-A</td>
<td>B</td>
<td>[14]</td>
</tr>
<tr>
<td>Memon et al. (2012)</td>
<td>40</td>
<td>Phase II</td>
<td>2-A</td>
<td>B</td>
<td>[12]</td>
</tr>
<tr>
<td>Rhee et al. (2008)</td>
<td>42</td>
<td>Phase II</td>
<td>2-A</td>
<td>B</td>
<td>[27]</td>
</tr>
<tr>
<td>Saxena et al. (2012)</td>
<td>48</td>
<td>Phase II</td>
<td>2-A</td>
<td>B</td>
<td>[28]</td>
</tr>
</tbody>
</table>

The GRADE system consists of four factors in strength of a recommendation: balance between desirable and undesirable effects, the quality of the evidence, values and preferences and, finally, costs.

NCI Grade 2-A: Non-randomized controlled trial – total mortality end point; NCI Grade 3-ii-A: Consecutive case series – total mortality end point. Grade evidence quality score (right-hand column) B: High-quality study; C: Low-quality study.

Evaluation of evidence taken from [29,30].
Figure 3. Treatment approach to liver metastases without extrahepatic spread (European Neuroendocrine Tumor Society consensus guidelines 2012).

†Recommendations from the working group on neuroendocrine liver metastases. IFN: Interferon; LITT: Laser-induced thermal therapy; LM: Liver metastases; RFA: Radiofrequency ablation; PRRT: Peptide receptor radionuclide therapy; RPVE: Right portal vein embolization; RPVL: Right portal vein ligation; SIRT: Selective internal radiotherapy; SSA: Somatostatin analog; TACE: Transarterial chemoembolization; TAE: Transarterial embolization.

Reproduced with permission from [7].

version 1.0) [11,12,14–16] and this compares favorably with the response rate observed with peptide receptor radionuclide therapy [17,18], as well as external beam radiotherapy [19–24]. There is also provisional evidence (in a small number of patients) that SIRT may be given following peptide receptor radionuclide therapy without an increased risk of radioembolization-induced liver disease [25,26].

Conclusion

Further prospective studies are required with SIRT in order to inform the management of liver-dominant mNETs, with consideration being given to the impact of this procedure on health-related quality of life as well as overall survival.

Financial & competing interests disclosure

A Kennedy has received research funding from Sirtex Medical Ltd. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References


Liver metastases from neuroendocrine tumors

SYMPOSIUM PAPER


STAY INFORMED...

Expertly distilling the latest developments in the patent literature

NOW LISTED ON MEDLINE

All articles indexed by:
MEDLINE®, Chemical Abstracts
EMBASE/Excerpta Medica

Pharmaceutical Patent Analyst

"This journal has become essential reading for those interested in the patent literature. It uniquely balances high-quality review articles with a holistic coverage of key topics in the changing world of patent law"

Senior Editor, Dr Lyn Jones (Pfizer)

Email us for your free 30-day trial!
Contact: trials@future-science.com
Visit: www.future-science.com
Evidence-based integration of selective internal radiation therapy into the management of cholangiocarcinoma

Laetitia Fartoux1 & Olivier Rosmorduc*,1

Cholangiocarcinoma (CC) is a hepatobiliary cancer with features of cholangiocyte differentiation. This rare cancer accounts for 3% of all gastrointestinal tumors, but its incidence rate is approximately 2000 new cases per year in France. CC can be classified anatomically as intrahepatic CC (iCC), perihilar CC and distal CC and it can also differ in epidemiology, etiology and treatment. iCC represents approximately 8% of cases of CC and its incidence and mortality rates have been increasing over the past 30 years (Figure 1)[1,2]. Several risk factors have been identified for iCC (i.e., hepatolithiasis, hepatitis B and C, cirrhosis, diabetes and primary sclerosing cholangitis), but most cases are sporadic [3]. iCC is divided into mass-forming, periductal-infiltrating and intraductal growth types. It frequently presents as an intrahepatic mass lesion with a progressive uptake of contrast during the venous phase. CA19-9, which may detect iCC with 62% sensitivity and 63% specificity, might also have a prognostic value. A definitive diagnostic of iCC requires a liver biopsy that identifies the presence of an adenocarcinoma or a mucinous carcinoma. Recent integrative genomic analyses have shown that there are two main biological classes of iCC with differing prognostic and therapeutic implications: first, the inflammation class (38%), which is characterized by activated inflammatory signaling pathways (STAT3), and second, the proliferation class (62%), which is characterized by the activation of oncogenic pathways (RAS, MAPK and MET) [4].

The treatment of choice for iCC is surgical resection, but fewer than 60% of patients survive for 5 years after resection, the median disease-free survival remains less than 26 months and the recurrence rate is between 60 and 65% [5]; moreover, the benefit of adjuvant chemotherapy has not been demonstrated so far [5]. The factors associated with recurrence include vascular invasion, cirrhosis, lymph node metastasis and multiple tumors [5,6]. Liver transplantation for iCC is highly controversial because of the high recurrence rate (~70% within 5 years) and a median disease-free survival of approximately 8 months [7]. Locoregional therapies, including intra-arterial therapy (IAT; i.e., transarterial chemoembolization, drug-eluting beads and bland embolization) or radiofrequency ablation, may be options for patients with unresectable tumors. However, data on the safety and efficacy of IATs for iCC are very limited. In a recent study, IATs were safe and led to stable disease or a response in up to three-quarters of patients with iCC and showed a median survival of 13.2 months, which did not differ based on the type of IAT (Figure 2) [8]. The standard of care for advanced-stage iCC is systemic chemotherapy using cisplatin and gemcitabine, which offers a median overall survival of 11.7 months [9]. Currently, no second-line chemotherapy has been validated due to the absence of large Phase III clinical trials, although a number of targeted therapeutics directed against several key signaling pathways, including EGFR, angiogenesis and the MAPK pathway, have been evaluated [10,11].

Keywords
• cholangiocarcinoma
• radioembolization
• selective internal radiation therapy
Evidence for selective internal radiation therapy

In a pilot study, 24 patients presenting with iCC were treated using selective internal radiation therapy (SIRT; or radioembolization) with yttrium-90 (Y-90) microspheres after failure of first- and second-line chemotherapy [13]. The median overall survival was 14.9 months and was associated with the following factors: Eastern Cooperative Oncology Group (ECOG) performance status, portal vein thrombosis and tumor morphology and distribution (i.e., 31.8, 6.1 and 1 for ECOG performance status 0, 1 and 2, respectively; 31.8 vs 5.7 months in the absence or presence of portal vein thrombosis, respectively; and 31.8 vs 5.7 months for patients with peripheral vs infiltrative tumor, respectively). On imaging follow-up, tumors showed a partial response in 27% of patients and stable disease in 68% of patients. Tolerance was acceptable, with fatigue and transient abdominal pain occurring in 75 and 10% of patients, respectively. Only one patient (4%) developed grade 3 hyperbilirubinemia. These results were confirmed in a series of 25 patients with more advanced disease (i.e., 40% of patients with ECOG performance status 1 or 2; 40% with infiltrative tumors; 48% with extrahepatic metastases; and 60% with hepatic tumor burdens of between 26 and 50% of the whole liver) [14]. In this study, the mean activity of Y-90 administered was 1.76 GBq and the percentage shunting to the lung was 4.4%. The median survival was 9.3 months, with two significant prognostic variables associated with improved survival: peripheral tumor type (vs infiltrative) and ECOG performance status (0 vs 1 or 2) [14]. These findings were confirmed in a subsequent retrospective analysis that found that statistically significant predictors for prolonged survival following SIRT were performance status, tumor burden and Response Evaluation Criteria In Solid Tumors (RECIST) response [15]. A more recent study with a similar number of patients showed a median overall survival of 11.5 months from the first SIRT procedure and of 25.1 months from the diagnosis of unresectable iCC. The tumor responses were as follows: complete response, 0%; partial response, 11%; stable disease, 68%; and progressive disease, 21%; with a median time to progression of 4.8 months [16]. Unexpectedly,
in this study, the presence of extrahepatic metastasis, multifocal tumor burden or bilobar distribution in the liver did not affect the median survival [8]. In terms of response, fluorine-18 fluorodeoxyglucose PET independently predicted survival in patients with iCC treated with Y-90 microspheres [17]. Indeed, the change at 3 months in metabolic tumor volume (but also changes in maximum or mean standardized uptake value) discriminated between patients with a longer and those with a shorter survival, even surpassing the predictive value of morphological criteria, such as those of RECIST or the European Association for the Study of the Liver (EASL). By contrast, pretherapeutic technetium-99m-labeled macroaggregated albumin scintigraphy was not a predictor for successful SIRT with Y-90 microspheres [17].

Finally, Y-90 microsphere therapy for the downstaging of patients with unresectable disease has also been reported [18,19]. Such a radiation lobectomy using Y-90 microspheres may also be a safe and effective technique for increasing the future remnant liver that is comparable with portal vein embolization from a bridge-to-resection perspective for iCC, as has been recently reported for hepatocellular carcinoma [20].

Conclusion
In conclusion, these different studies provide evidence that SIRT using Y-90 microspheres may be a safe and efficacious treatment option for unresectable iCC, particularly in patients without symptoms or with minor cancer-related symptoms (ECOG performance status 0 or 1) and with peripheral, noninfiltrative tumors. In the absence of any other effective treatment in the second-line setting, these results warrant further prospective investigation.

Financial & competing interests disclosure
O Rosmorduc has received honoraria from Roche, Bayer and Sirtex Medical Ltd. L Fartoux has received honoraria from Bayer and BMS. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.
References

Evidence-based integration of selective internal radiation therapy into the management of breast cancer liver metastases

Roberto Cianni*1 & Giuseppe Pelle1

Breast cancer is the third most frequent cancer worldwide and the most common malignancy in women. The mortality:incidence ratio is approximately 61%, making breast cancer the leading cause of cancer deaths in women worldwide (~314,000 deaths annually, representing 14.1% of all cancer deaths in females). Incidence rates are high in almost all of the developed countries, with the highest age-standardized incidence in the USA (87.1 per 100,000) [1]. Liver metastases are present in at least 10–15% of patients with advanced breast cancer, with the liver representing the most common site of life-threatening disease progression, along with the lung and brain. Approximately 4–5% of metastatic breast cancer patients develop liver-only disease. Standard treatments for advanced breast cancer in the liver are systemic chemotherapy, hormone therapy and surgery. Although surgery can prolong survival, only a small percentage of patients (10–20%) with advanced liver-dominant breast cancer are eligible for resection of liver metastases [2].

Selective internal radiation therapy (SIRT; or radioembolization) is a minimally invasive procedure that uses resin- or glass-based microspheres loaded with yttrium-90 (Y-90). Y-90 is a high-energy β-emitter with a half-life of 64 h that delivers very high localized doses of β-radiation (>100 Gy) with limited penetration (median: 2.5 mm; maximum: 11 mm) to the surrounding normal hepatic parenchyma. The intra-arterial administration of Y-90 microspheres takes advantage of the preferential arterial blood supply to the hepatic tumors, in contrast with the prevalent portal venous supply to the normal hepatic parenchyma. This is particularly true for metastases from breast cancer that frequently exhibit a high degree of arterial neovascularization. For this reason, higher doses of radiation can be administered with intra-arterial SIRT compared with external beam radiation therapy, without inducing a high proportion of life-threatening complications, such as radiation-induced liver disease [3,4]. For this reason, SIRT is preferred over external beam radiation therapy, during which even a low-dose of radiation (30 Gy) may be responsible for an indiscriminate irradiation to the liver and hepatic insufficiency in a high percentage of patients (50%) [5,6].

Evidence for SIRT in breast cancer

Different studies have shown that SIRT is effective and safe when used for the treatment of chemotherapy-refractory advanced breast cancer in patients with liver-dominant metastases [4,7,8]. Despite the limited number of patients included in these studies, seemingly clinically relevant prolongation in survival accompanied by high response rates have been recorded in patients who have failed at least two lines of chemotherapy [4,7,8].

Over the last 8–9 years, we have treated 671 patients with SIRT, including 14% of patients with liver-dominant metastatic breast cancer. In 2013, we published our experience of our first 52 breast cancer patients [8]. Notably, we observed a high response rate at the first follow-up (8 weeks post-SIRT) with a partial response (PR) as assessed by Response Evaluation Criteria in Solid Tumor...
(RECIST) in 56% of patients. Times to progression in the liver and overall were 8.4 and 6.4 months, respectively, thereby demonstrating significant liver lesion control compared with control of extrahepatic disease following SIRT. In this case series, the median overall survival was 11.5 months and was better in those whose performance status and liver function were preserved compared with those with a worse prognosis (14.3 vs 8.2 months). Notably, based on our now extensive experience with SIRT for the management of liver metastases, since 2011, we no longer conduct pre-SIRT technetium-99m-labeled macroaggregated serum albumin scintigraphy because the incidence of extensive liver–lung shunting (>20%) in patients with a tumor burden >20% in the liver is very low. Instead, we rely on pre-SIRT fluorine-18 fluoro-deoxyglucose PET–computed tomography integrated imaging and digital rotational angiography (DynaCT; Siemens Healthcare, Germany) for the 3D analysis of lesion vascularization, the identification of any aberrant vessels to the upper GI tract and to predict the distribution of Y-90 resin microspheres. All of the patients with bilobar metastasis are treated by sequential separate lobar treatments with 4–6-week intervals between the procedures. Y-90-PET is then conducted immediately after each procedure in order to assess the distribution of microspheres in the lesion. Approximately 5 weeks after the first SIRT procedure, changes in the functional tumor volume from baseline are calculated using fluorine-18 fluoro-deoxyglucose PET volume computer-assisted reading (GE Healthcare, WI, USA), which provide an important early predictor of response and guide subsequent SIRT planning of the contralateral lobe in patients with bilobar disease (Figure 1).

Our initial experience reflects the published evidence from other centers in heavily pretreated and chemoresistant patients. In a prospective study of 30 breast cancer patients with treatment-refractory liver metastases treated with Y-90 resin microspheres, Jakobs et al. reported a median overall survival of 11.7 months, with a trend towards longer survival in patients without extrahepatic disease compared with those with extrahepatic disease (16 vs 9.6 months) [4]. This study reported a high PR rate as assessed by RECIST of 61% and stable disease (SD) in a further 35% of patients, resulting in a median overall survival of 23.1 months in partial responders versus 5.7 months in nonresponders. In 2007, Coldwell et al. reported encouraging results in the treatment of 44 breast cancer patients with hepatic lesions using Y-90 resin microspheres [7]. All of the lesions were found on angiography to be hypervascular and considered to be excellent candidates for SIRT. Upon imaging at 12 weeks post-SIRT, response rates as assessed by RECIST were 41% for PR, 47% for SD and 5% for progressive disease. When the authors performed a follow-up by PET–computed tomography, 95% of patients had a PR and 5% had a SD.

The most clinically important complication of SIRT is hepatic failure, which may be life-threatening. Predisposing factors for this complication are impaired liver function (total bilirubin >2 mg/dl) and an Eastern Cooperative Oncology

Figure 1. Pre- and post-treatment fluorine-18 fluoro-deoxyglucose PET in a patient who received sequential lobar selective internal radiation therapy. Treatment was initially administered to (A) the right then (B) the left lobe.

FTV: Functional tumor volume; PFS: Progression-free survival; SIRT: Selective internal radiation therapy
Group (ECOG) performance status of greater than 2. Other adverse events are cholecystitis and gastroduodenal ulcers caused by radiation-related inflammation following unintended delivery of the microspheres to the GI tract. Minor complications include postprocedural abdominal pain and nausea, which usually resolve spontaneously or after standard medications.

**Conclusion**

SIRT with Y-90 resin microspheres appears to be an effective procedure for the treatment of liver metastases from breast cancer in the salvage setting. Clinically relevant survival and high response rates have been demonstrated in patients with treatment-refractory disease, particularly in those with limited liver involvement and preserved performance status. In our opinion, survival is comparable or even superior to an effective chemotherapy line in these chemoresistant patients. Most patients responding to SIRT are offered further lines of treatment, since disease control in the liver may change the prognosis of the patient from poor to fair. The ‘one-size-fits-all’ model should no longer be used in metastatic breast cancer, with individualized approaches to care depending on the patient’s performance status and disease profile. Multicenter Phase II/III trials are needed for the prospective evaluation of SIRT as a first- or second-line approach in combination with chemotherapy and/or hormonal therapy, with consideration being given to the sequence of treatment in patients with aggressive versus indolent disease.

**Financial & competing interests disclosure**

R Cianni has received lecture and consulting fees from Sirtex Medical Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The authors would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

**References**

Your dedicated resource for a new era of healthcare

Journal of Comparative Effectiveness Research

Citations:
EMBASE/Excerpta Medica, EMCare, MEDLINE/Index Medicus, Journal Citation Reports/Science Edition, Science Citation Index Expanded (SciSearch®)

“With an accelerating comparative effectiveness research agenda, there will be a growing need for peer-reviewed publication of this research. The Journal of Comparative Effectiveness Research will be uniquely positioned and is very timely.”

Robert W Dubois, Associate Editor, National Pharmaceutical Council, USA

Email us for your free 30-day trial!

Contact: trials@futuremedicine.com
Visit: www.futuremedicine.com
Evidence-based integration of selective internal radiation therapy into the management of ocular melanoma liver metastases

Brian Stedman*

Cutaneous melanoma and ocular melanoma (OM) both derive from melanocytes, but show remarkably different tumor biology [1]. Primary cutaneous melanoma is relatively common compared with OM, resulting in surgical R0 resection in 98% of cases [2]. The disease can spread to any organ via the lymph and blood, with hepatic metastases occurring in less than 10% of cases. OM, by contrast, is relatively uncommon and also occurs in a young population (median age at diagnosis is 55 years). Approximately 80% of intra-OMs arise in the choroid, 5% in the iris and 15% in the ciliary body [1]. The eye has no lymphatics and so most (80%) of the 50% of patients who develop metastases through hematoogenous spread have liver-dominant disease [3].

The optimal treatment of the primary tumor remains controversial. Evidence from Collaborative Ocular Melanoma Study (COMS) report number 28 showed that 5-year survival was similar (~90%) whether the primary tumor was treated with enucleation or 125I brachytherapy [4]. Alternatively, the tumor can be treated using eccentric placement of ruthenium plaques and proton beam therapy [5], with enucleation only being necessary when complications occur (e.g., retinal detachment or proliferative vitreoretinopathy) or due to persistence of the irradiated tumor within the eye [6]. Regardless of the treatment approach adopted for the primary tumor, the outcome appears to be similar. Prognosis is primarily determined by tumor stage at diagnosis [7], with genetic alterations (e.g., monosomy 3) having a marked impact on survival [8]. Based on these parameters, the Liverpool Uveal Melanoma Predictor Online (‘LUMPO’) is a useful tool for prognostication in OM and for the triage of patients for regular follow-up [9,10].

A recently published paper by Marshall et al. recommended regular MRI every 6 months for the early detection of hepatic metastases for high-risk patients with uveal melanoma [11]. Once hepatic metastases occur, the prognosis is bleak, with 10% survival rates at 1-year despite aggressive treatment and with little change in mortality over the last three decades [12]. Furthermore, there are no effective systemic treatments. Even with 6-monthly MRI, only 14% of patients are amenable to resection [11] and 50% of patients will die with liver-only disease. This somewhat nihilistic view nevertheless provides a compelling argument for locoregional treatment in order to control the progression of OM metastases in the liver [13].

Locoregional treatment: results from the literature & personal experience

- Transarterial chemoembolization

Evidence from published studies over the last two decades show that overall survival following transarterial chemoembolization (TACE) varies between 6 and 11 months [13], with better survival occurring with immunoembolization (using GM-CSF) [14] or in studies in patients with limited disease in the liver [15]. A key determinant of survival following TACE is the distribution of disease

*Lead Interventional Radiology, Lead Upper Gastrointestinal Cancer Network, Southampton University Hospital NHS Trust, Tremona Road, Southampton, Hampshire, SO16 6YD, UK; Tel.: +44 23 8077 7222; brian.stedman@uhsc.nhs.uk

KEYWORDS
- ocular melanoma
- percutaneous hepatic perfusion
- radioembolization
- selective internal radiation therapy
- transarterial chemoembolization
in the liver, with a nodular angiographic pattern being associated with favorable response and median survival of more than 2 years, while an infiltrative angiographic (so called ‘measles’) pattern (Figure 1) being associated with a median survival of 4 months [16]. Although survival is lengthened with TACE, most patients eventually progress.

Currently, there is limited evidence for TACE using drug-eluting beads (DEB-TACE) in OM. In a Phase II study of ten patients who had previously been treated with enucleation (eight cases), radiotherapy (one case) or both (one case) for the primary tumor followed by systemic immunotherapy or chemotherapy for liver metastases, all patients were alive after a median follow-up of 6.5 months following treatment with DC Beads® (BTG International Ltd, London, UK) loaded with irinotecan [17]. Results from a further study of DEB-TACE loaded with doxorubicin in 20 patients with liver metastases from melanoma are expected to be published shortly (NCT01409733). Our experience using DEB-TACE selectively in patients with unilobar localized nodular disease is encouraging, although our main concern is the impact of this treatment on the normal parenchyma, specifically biliary injury.

● Fotemustine
A further retrospective, single-center study was conducted in 21 patients with hepatic metastases treated by palliative TACE with the alkylating agent fotemustine. This study found that the mean survival was 28.7 months following fotemustine dissolved in lipiodol [18]; however, this agent is not available in the UK. While these initial results appear encouraging, further prospective studies are clearly needed in order to confirm the findings from this study.

● Chemosaturation therapy with percutaneous hepatic perfusion
Isolated hepatic perfusion has been used for the treatment of malignant melanomas in the liver for a number of years [19]. A percutaneous alternative to isolated hepatic perfusion is chemosaturation therapy using percutaneous hepatic perfusion (PHP; from Delcath Systems, Inc., NY, USA) [20]. The Achilles’ heel of this approach is the induction of profound hypotension despite the use of systemic vasopressors for blood pressure support [21]. These vasopressors in turn can cause spasms of the hepatic artery, increasing the problems of administering chemotherapy. In a randomized controlled trial comparing PHP (n = 44) with best alternative care (n = 49; NCT00324727), progression-free survival was significantly prolonged (8.0 vs 1.6 months; p < 0.001); however, overall survival between the two groups was similar (perhaps in part due to the large number of patients [55%] who crossed over to the active treatment arm) [22]. The most common toxicities in best alternative care-to-PHP crossover patients were hematological, including periprocedural thrombocytopenia (71%) and anemia (57%), as well as melphalan-related neutropenia (82%) and thrombocytopenia (79%). In September 2013, the US FDA refused a new drug application for this treatment [23], mainly due to the high mortality rates (7% in 122 patients) and severe hypotension associated with this therapy [24].

● Selective internal radiation therapy
Since the first published retrospective series on selective internal radiation therapy (SIRT) in OM in 2009 [25], two other case series have been published on this procedure in liver-dominant OM [26-27]. In the first of these case series, 32 patients with liver metastases from OM received SIRT with Y-90 resin microspheres after failing immunoembolization or TACE [26]. The median overall survival was 10.0 months and was significantly extended in patients who had a pretreatment tumor burden in the liver of less than 25% compared with 25% or greater (10.5 vs 3.9 months; p = 0.0003). In a second case series, a total of 134 SIRT procedures were performed in 71 patients with unresectable liver metastases from uveal melanoma [27]. Fifty-eight patients (82%) received SIRT as a salvage therapy. The median overall survival was 12.3 months (range: 1.9–49.3 months) after SIRT, equating to a median survival of 23.9 months (range: 6.2–69.0 months) after diagnosis of liver metastases.

Figure 1. Infiltrative pattern of liver metastases from ocular melanoma.
Conclusion
The primary management of OM does not affect survival; however, MRI at 6-monthly intervals is especially valuable in high-risk patients. Early resection or ablation of liver metastases is recommended where possible. Laparoscopy is important for establishing the extent of bulky disease. Before considering locoregional management, key factors to consider are the patient’s performance status and cardiac risk factors (especially for PHP), as well as the extent and distribution of the disease in the liver. SIRT is well tolerated and allows for whole-liver disease control. More safety data are still needed on DEB-TACE, but this technique may allow for the control of nodular disease. The Delcath PHP procedure is awaiting further safety data and refinements (and although it is approved in Europe, it should be avoided in patients with a high risk of complications). Finally, future work is needed on the impact of chromosomal abnormalities on responses to treatment [28].

Financial & competing interests disclosure
B Stedman is a proctor on the medical advisory boards and received honoraria for speaking at congresses from Sirtex Medical Ltd and Delcath Systems, Inc. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References
22 Alexander HR; on behalf of the CS-PHP Investigators. Percutaneous hepatic perfusion (PHP or ChemoSat) with melphalan versus best alternative care (BAC) in patients (pts) with hepatic metastases from melanoma: a post hoc analysis of PHP-randomized versus...
BAC-to-PHP crossover versus BAC-only pts. 

23 Delcath receives complete response letter from 
FDA for Melblez™ kit new drug application. 
http://phx.corporate-ir.net

24 FDA Briefing Document: Oncologic Drugs 
Advisory Committee Meeting, 2 May 2013, 
NDA 201848–001: Melblez Kit, Delcath 
Systems, Inc. 
www.fda.gov

25 Kennedy AS, Nutting C, Jakobs T et al. A 
first report of radioembolization for hepatic 
metastases from ocular melanoma. *Cancer 

26 Gonsalves CF, Eschelman DJ, Sullivan KL, 
Anne PR, Doyle L, Sato T. Radioembolization 
as salvage therapy for hepatic metastasis of uveal 
melanoma: a single-institution experience. 

27 Eldredge-Hindy H, Ohri N, Anne PR et al. 
Yttrium-90 microsphere brachytherapy for 
liver metastases from uveal melanoma: 
clinical outcomes and the predictive value of 
fluorodeoxyglucose positron emission 
coc.0000000000000033 (2014) (Epub ahead 
of print).

28 Field MG, Harbour JW. Recent developments 
in prognostic and predictive testing in uveal 
Cost of selective internal radiation therapy versus other modalities

Harpreet S Wasan*

Evaluation of comparative effectiveness and cost-effectiveness is an essential component in the integration of new technologies into medical management, with data from prospective clinical trials (e.g., health-related quality of life using validated tools) being mandated by most health authorities. Health economics has its own vocabulary and so a glossary of terms is provided in Table 1 for the uninitiated.

One of the key issues in assessing the comparative costs and cost-effectiveness of locoregional therapies for primary and secondary cancers in the liver is the limited number prospective trials. Health economic models, however, are valuable tools for overcoming such limitations that bring together information from different sources in order to assess the expected costs and outcomes. Such information is essential for healthcare reimbursement agencies and payers at national, regional and local levels when making funding decisions in order to ensure that the allocation of limited resources is optimized.

Selective internal radiation therapy versus conventional transarterial chemoembolization

One of the most detailed studies comparing the cost-effectiveness of selective internal radiation therapy (SIRT) versus conventional transarterial chemoembolization (TACE) was conducted by a group from Cleveland (OH, USA) in patients with unresectable hepatocellular carcinoma (HCC) [1]. This study recorded significantly greater costs associated with conventional TACE than SIRT, largely due the greater number of mean hospital days for the initial procedure (3.5 ± 0.7 vs 0.5 ± 0.2; p < 0.001) and for readmissions (7.9 ± 1.7 vs 3.6 ± 0.6; p = 0.03) with TACE. While the rates of postembolization syndrome were similar between the procedures in this study, the severity of postembolization syndrome was significantly worse with TACE, as would be expected from a purely embolic approach, and required additional hospitalization and treatment in a significantly greater number of patients compared with SIRT (p = 0.02) [1]. Otherwise, there were no significant differences between the groups in major or minor complication rates (p = 0.58) or 30-day mortality (p = 0.07) [1].

Subsequently, a systematic review of the literature examining the comparative safety and effectiveness of SIRT and conventional TACE for the treatment of HCC concluded that the two procedures had a similar efficacy (defined by tumor response and patient survival), with significantly longer time to progression and lower toxicity with SIRT [2]. Compared with SIRT, the meta-analysis found that conventional TACE was associated with a statistically greater overall toxicity, as well as a higher rate of abdominal pain and hepatic transaminase elevation postprocedure. Numerous studies have also consistently observed a significantly shorter postprocedure hospital stay with SIRT compared with conventional TACE [2]. Although conventional TACE costs less in the majority of cases, SIRT was less expensive in 33.4% of cost analysis simulations that compared the two procedures [2].

KEYWORDS
• cost-effectiveness • QALY
• radioembolization
• selective internal radiation therapy • transarterial chemoembolization

*Department of Cancer Medicine, Hammersmith Hospital/Imperial College London, London, UK; h.wasan@imperial.ac.uk
This, in part, reflects the significantly fewer treatments required with SIRT compared with TACE (median: 1 vs 3.4 in a recent prospective Phase II comparative pilot study [3]).

**SIRT versus doxorubicin-loaded DC Beads®/doxorubicin-loaded irinotecan-eluting beads**

Currently, there are no direct comparative studies of SIRT versus drug-eluting bead (DEB) TACE. However, recent analyses have shown that the relative cost per patient of SIRT appears to be similar to a median of 3.4 procedures with DEB-TACE using either doxorubicin-loaded DC Beads® (DEBDOX; BTG International Inc., PA, USA) or irinotecan-loaded drug-eluting beads (DEBIRI; Table 2).

**SIRT versus best supportive care**

The cost–effectiveness of SIRT compared with best supportive care (BSC) for the treatment of metastatic colorectal cancer in chemotherapy-refractory patients has also been modeled both from the perspective of the UK NHS [4,5] and from the payer perspective in Italy [6]. The models integrated the survival data from a comparative retrospective cohort study of yttrium-90 resin microspheres versus BSC in chemotherapy [7]. With short-term survivals for the patients with end-stage disease, improvements in quality of life are key considerations. Using quality of life measurements from a recent NICE economic evaluation in metastatic colorectal cancer, quality of life was assessed over the life horizon of the patients both prior to progression and after progression. Factored into these analyses were the toxicities associated with the intervention(s) before and after progression, as well as the costs of the interventions.

The results showed an increase in overall survival for patients receiving SIRT compared with BSC by a mean of 1.12 and 1.35 life-years in the UK and Italy, respectively, with a corresponding increase in quality-adjusted life-years (QALYs) of 0.81 and 0.83, respectively. Incremental costs of SIRT versus BSC in the UK and Italy were estimated to be £22,757 and €24,626, respectively, due to the cost of SIRT treatment as well as the costs associated with extension to life. The cost per QALY was estimated at £28,216 and €29,850 in the UK and Italy, respectively. Sensitivity analyses showed that the model was...
Cost of selective internal radiation therapy versus other modalities

SYMPOSIUM PAPER

Table 3. Comparison of the cost and cost-effectiveness (cost per quality-adjusted life-year [€] vs best supportive care) of selective internal radiation therapy and systemic treatment for the management of metastatic colorectal cancer.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment cost/patient (€)</th>
<th>Cost/QALY (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRT using yttrium-90 resin microspheres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17,390 (UK) [4]</td>
<td>33,457 (vs BSC) (UK) [4]</td>
<td></td>
</tr>
<tr>
<td>15,942 (Italy) [6]</td>
<td>29,850 (vs BSC) (Italy) [6]</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>45,692 (first line) [10]</td>
<td>182,044 (vs BSC) [11]</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>28,962–49,144 [8]</td>
<td>105,298 cost/QPFS (+ capecitabine vs capecitabine alone)</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>19,004 [12]</td>
<td>Regorafenib – cost: 70,920; QALYs: 0.47</td>
</tr>
</tbody>
</table>

†GBP = €1.18576, mid-market rate as assessed on 17 December 2013.
Bevacizumab dose: 75 mg every 3 weeks.
BSC: Best supportive care; QALY: Quality-adjusted life-year; SIRT: Selective internal radiation therapy.

robust to changes in parameters. Moreover, this cost per QALY compared favorably with the cost per QALY for new systemic chemotherapies (many of which are not available on the NHS due to their costs, especially in the setting of end-of-life care; Table 3) [6,8–14].

Conclusion
Health economic analysis has shown that SIRT (used as a one-off procedure) is effective and well tolerated and is less costly and more cost effective than other more widely used forms of liver-directed therapy or systemic treatment for HCC and colorectal cancer liver metastases. In HCC, the spectrum of SIRT can also encompass patients with portal vein thrombosis, which highlights its unique mechanism of radiation delivery to the tumor rather than an embolic process, as conventional TACE or DEB-TACE is contraindicated in this group.

Financial & competing interests disclosure
HS Wasan has the following disclosures: Sirtex Medical Ltd, Merck KGaA and Pfizer (advisory board member/speaker and research funding); Sanofi Aventis, Roche and Bayer (advisory board member/speaker); and CRUK, MRC and BRC-Imperial (research funding). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.

References


SYMPOSIUM PAPER

How does selective internal radiation therapy compare with and/or complement other liver-directed therapies?

Irene Bargellini*

Interventional oncology is one of the fastest-growing fields of radiology, with a range of minimally invasive, image-guided tumor therapies available and in development. These therapies include liver-directed arterial therapies (e.g., transarterial chemoembolization [TACE], drug-eluting beads [DEBs] and selective internal radiation therapy [SIRT]) and nonarterial therapies (e.g., percutaneous ablative therapies, intensity-modulated radiation therapy and image-guided radiation therapy) [1]. Transarterial therapies induce tumor cell killing through a variety mechanisms, from ischemia, ischemia combined with regional chemotherapy or brachytherapy/radiation therapy, by the selective injection of differently sized particles into the arteries supplying the tumors.

Comparison of SIRT & TACE

Compared with TACE, the pretreatment work-up for SIRT is slightly more involved, requiring a larger yttrium-90 team including interventional radiologists, nuclear medicine specialists and medical physicists [2]. However, the increased cost of each SIRT procedure is counterbalanced by the need for fewer treatment procedures [3] and hospital days postprocedure [4] due to a lower incidence of complications (particularly postembolization syndrome) with SIRT compared with TACE [5]. In our experience, patients appear to tolerate SIRT better than TACE, enabling the treatment of large lesions and also elderly patients with SIRT [6]. Comparisons of SIRT versus conventional TACE have mainly been conducted in hepatocellular carcinoma (HCC). A prospective trial comparing SIRT (n = 29) and TACE (n = 27) in HCC using the Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) questionnaire concluded that “despite the more advanced disease of patients who received SIRT, patients had a significantly better quality of life, based on social well-being (p = 0.019), functional well-being (p = 0.031), and embolotherapy-specific scores (p = 0.018)” [7].

Notably, a retrospective study from Northwestern Memorial Hospital (IL, USA) evaluating data from 463 patients with HCC who were treated with transarterial locoregional therapies (chemoembolization or radioembolization) over a 9-year period found that SIRT was associated with a longer time to progression than TACE (8.4 vs 13.3 months; p = 0.023) [8]. In another direct comparative study, more patients treated with SIRT than TACE were downstaged from United Network for Organ Sharing (UNOS) T3 to T2 (31 vs 58% patients; p = 0.023) [9]. However, other direct comparative studies (mainly with conventional TACE) have shown similar tumor responses [3] and overall survival rates [5,8] in HCC, cholangiocarcinoma [10] and liver-dominant neuroendocrine tumors [11] with these two treatment modalities.

Today, there is an increasing use of DEB-TACE, which, at least in the setting of HCC, is associated with reduced liver toxicity, improved tolerability and reduced postembolization syndrome [12]. Recently, encouraging results have been published with DEBs and irinotecan-preloaded therapy (DEBIRI) in selected patients with liver-dominant metastatic colorectal cancer (mCRC) [13–15].

Keywords

- cholangiocarcinoma
- embolization
- hepatocellular carcinoma
- intra-arterial
- liver metastasis
- yttrium-90

*Diagnostic & Interventional Radiology, Pisa University Hospital, Via Paradisa 2, 56100 Pisa, Italy; Tel: +39 050 996961; Fax: +39 050 995545; irenebargellini@hotmail.com

10.2217/FON.14.236 © 2014 Future Medicine Ltd
However, periprocedural complications (most notably pain) can be severe with DEBIRI [13], requiring particular attention in the management of pain [16]; this adds a further level of complexity to this procedure. Moreover, it is likely that patients would respond less well to localized, targeted chemotherapy (even with DEBIRI) in the chemorefractory setting if they are already refractory to the same chemotherapy formerly given as a systemic therapy. Thus, in this specific clinical scenario, SIRT becomes appealing as an alternative to chemotherapy.

**The complementary role of SIRT & TACE**

Given that disease is a dynamic process, the treatment approach needs to be adapted to meet changing clinical circumstances for each patient [17]. Published studies carried out in series of patients with neuroendocrine tumor metastases in the liver and also HCC have shown that treatment with SIRT is not precluded by prior nonradioactive embolization procedures [18–20]. Indeed, progression after TACE has been suggested to be one potential indication of SIRT in HCC patients [18].

However, prior embolization can activate parasitic arteries, thereby contraindicating SIRT (see the case illustration in Figure 1). For this reason, we would recommend that, in selected cases such as patients who are likely to respond poorly to TACE (e.g., patients with large HCC lesions), SIRT should represent the first treatment option, saving transarterial (chemo)embolization for those areas of persistent viable tumor after treatment. Accordingly, HCC patients with branch or segmental portal vein neoplastic thrombosis could be approached with SIRT, completing the treatment with TACE or percutaneous ablation, as needed.

The integration of different locoregional therapies can also be applied in the setting of liver metastasis. Hoffmann et al. described a cohort of 44 patients who received single-session whole-liver SIRT (mean activity: 2.13 GBq) for the management of liver metastases [21]. In these patients, SIRT resulted in a substantial decrease in tumor load in five patients (3/5 breast cancers, 1/5 colorectal cancers and 1/5 pancreatic cancers), thereby enabling radiofrequency ablation of the residual disease [21].

**Synergism between liver-directed therapies: the need for a new treatment algorithm**

A new treatment algorithm is clearly needed based on the collective experience of specialist units in order to provide guidance regarding the relative utility of locoregional treatments, used in sequence, for the management of primary and secondary liver tumors. While there are few published data on this topic, “not everything that counts can be counted, and not everything that can be counted counts,” as William Bruce Cameron so wisely noted in 1963 [22]. The key to effective care is “the ability to use our clinical skills and past experience to rapidly identify each patient’s unique health state and diagnosis, their individual risks and benefits of potential interventions and their personal values and expectations” [23].

The significant heterogeneity of patients with intermediate (Barcelona Clinic Liver Cancer [BCLC] stage B) HCC has led to the publication of a proposed subclassification by Bolondi et al. in order to facilitate treatment decisions for BCLC stage B HCC [24]. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 are divided into those beyond Milan criteria and within up-to-seven criteria (‘good’ intermediate stage) [25,26] and those with greater tumor burden (‘poor’ intermediate stage). In the setting of a ‘good’ intermediate stage, those patients who are potential candidates for transplantation could benefit from SIRT as a more efficient downstaging treatment modality compared with TACE [9]. In addition, patients at a ‘poor’ intermediate stage are less likely to respond properly to TACE and, for this reason, SIRT represents a more appealing treatment option. In our Institution, SIRT is also recommended for patients with liver-dominant, metastatic, chemotherapy-refractory disease, followed by other localized treatments (as needed).

Due to the relatively low incidence and the heterogeneity of presentation of cholangiocarcinoma, it is difficult to propose a treatment algorithm in this setting. However, today, based on our limited experience with SIRT, we use SIRT as a consolidation treatment following first-line chemotherapy (before disease progression). Nevertheless, each treatment is planned in the setting a multidisciplinary tumor board that necessarily has to include surgeons, oncologists and interventional radiologists [27].

**Discussion**

With a few exceptions [28,29], the lack of published data on the relative cost-effectiveness of various liver-directed treatments for end-of-life
care remains one of the biggest challenges to the development of clinical guidance in this area. There are few published cost–effectiveness analyses on surgery [30–32], despite the recognized value of R0 resection in prolonging survival and progression-free survival for patients with liver tumors. Even though the incidence is low (between 1 in 30 to 1 in 50 patients), the downstaging of patients with liver-dominant mCRC with second or third treatments such as SIRT can have significant impacts on the cost–effectiveness of these treatments. Prospective evaluations are now ongoing as part of the FOXFIRE study in order to evaluate the cost per quality adjusted life-year (QALY) of SIRT in the first-line setting for the management of unresectable, liver-dominant mCRC [33]. However, further studies are needed on the long-term outcomes of surgery post-SIRT and the requirement for adjuvant treatment in such patients (with supporting pathologies of resected tissue).

A prospective audit is ongoing in the UK (starting in January 2014) in order to evaluate the effectiveness of SIRT based on the outcomes of 200 procedures [34]. The NICE limit of £35,000 per QALY is conservative, especially for end-of-life care, in which up to a third of the costs of care are used in the last 30 days of life. Clearly, the benefit for any effective treatment or procedure will be greatest (in terms of cost per QALY) earlier in the treatment process rather than as a salvage treatment.

**Resolving conflicts within the multidisciplinary team**

Conflicts within multidisciplinary teams (MDTs) on the relative value of surgical versus locoregional treatment, for example, can often be resolved over time by using an annual audit of difficult cases where the treatment decision is evaluated in the context of the eventual outcome for the patient [35]. However, no strategy is foolproof, and the strength of a MDT is its flexibility in adopting alternative approaches if the patient progresses.

**Is there a lesion size limit for SIRT?**

In intermediate-stage HCC in patients without portal vein thrombosis (PVT) and good liver function and appropriate vascularity, there is no limit to the size of lesion treated by SIRT, provided that the functional liver reserve is not exceeded. For advanced-stage HCC with PVT, patients are usually excluded if there is invasion of the main portal vein, thereby limiting the use of SIRT to those who are likely to have the best outcomes. In young patients, SIRT may also be combined with sorafenib. If there are concerns over the tolerability of SIRT, then sequential lobar treatment may be considered.

**Sequential TACE & SIRT**

There are no high-quality published data on the relative value of conducting TACE before SIRT or vice versa. The treatment decision should be based on the tumor burden and the treatment intent (i.e., TACE is a good option if the treatment intent is cytoreduction and the tumor burden is not too high, while SIRT could be a better option for downstaging). Locoregional therapies should not be viewed as competitors in the management of liver tumors, but rather are tools that are often used sequentially in order to optimize the outcomes for patients. Percutaneous ablation and TACE, for example, are frequently used in combination for the management of the same lesion or for the management of different lesions during the same treatment session (depending on the size of the lesion). The combination of ipsilateral SIRT with superselective transarterial embolization (TAE) (for small nodules) is also possible within the same session.
SIRT in combination with radiosensitizing chemotherapy

In the chemotherapy-refractory setting, it may be appropriate to consider SIRT alone or in combination with chemotherapy, depending on the performance status of the patient. However, SIRT should always be combined (either together or sequentially) with systemic chemotherapy for the management of liver-dominant, unresectable mCRC (as well as cholangiocarcinoma) in the first- or second-line setting in order to maximize the treatment response. This is even more important in BRAF-mutant patients, for example, where the outcome with chemotherapy alone is likely to be poor, although further evidence of the outcomes of SIRT in these patients is still needed. Overall, the use of SIRT as a consolidation therapy to first- or second-line therapy in patients with liver-dominant mCRC would seem a logical approach (especially if the disease does not show an aggressive clinical course with the rapid development of metastases beyond the liver).

Recommended time between the cessation of biological therapy & SIRT

Cetuximab

The recommended time between the cessation of biological therapy and SIRT is an important consideration, as many patients with mCRC are treated with cetuximab in the salvage setting. Cetuximab is a powerful radiosensitizer, but has a very short half-life. There are no published safety studies of cetuximab and SIRT; however, based on our experience, we would recommend stopping cetuximab at least 4 weeks in advance of SIRT.

Bevacizumab

A recent study of bevacizumab-treated individuals in the neoadjuvant setting showed no increase in perioperative complications (when treatment was stopped 5–6 weeks before liver resection), although the effects of bevacizumab treatment on circulating and local VEGF at the time of liver resection were still evident [36]. We would recommend stopping bevacizumab at least 6 weeks prior to SIRT. In addition to problems of vascular pruning, which may make the SIRT procedure more difficult, bevacizumab is also a radiosensitizer (with a long half-life) and there is no protocol for bevacizumab with radiotherapy in any cancer. Currently, studies are only evaluating bevacizumab when given after SIRT.

Sorafenib

Sorafenib is also a potent radiosensitizer, but has a shorter half-life than bevacizumab. The observations from a number of practices is that sorafenib does not cause the same level of vascular pruning as bevacizumab. It is also important to note that the pathology of angiogenesis in mCRC and HCC is also likely to be different, and this may explain the different effects of these two treatments.

Conclusion

SIRT should be considered as an integral part of the care of patients with liver-dominant tumors, which is likely to have a beneficial effect when combined with the range of systemic and other liver-directed therapies (with differing mechanisms of action) in order to optimize the outcomes for patients.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

The author would like to thank Rae Hobbs (of Scribe Medical) for her editorial assistance in the development of this paper, funded by Sirtex Medical Ltd.
How does SIRT compare with &/or complement other liver-directed therapies?  

**SYMPOSIUM PAPER**

Radioembolization in patients with unresectable hepatocellular carcinoma.  

6 Golferi R, Bilbao JI, Carpanese L et al.  
Comparison of the survival and tolerability of radioembolization in elderly vs. younger patients with unresectable hepatocellular carcinoma.  

7 Salem R, Gilberstein M, Butt Z et al.  
Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization.  

8 Salem R, Lewandowski RJ, Kulik L et al.  
Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma.  

9 Lewandowski RJ, Kulik LM, Riaz A et al.  

10 Hyder O, Marsh JW, Salem R et al.  

11 Yang TX, Chua TC, Morris DL.  
Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases – a systematic review.  

12 Lammer J, Malagari K, Vogl T et al.  

13 Martin RC, Joshi JF, Robbins K et al.  
Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of a multi-institutional study.  

Transarterial chemoembolization using DEBIRI for treatment of hepatic metastases from colorectal cancer.  

15 Fiorentini G, Aliberti C, Tilli M et al.  
Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a Phase III study.  

16 Marques A, Garcia R, Gomez F, Giammaria F.  
Ultrasound-guided paravertebral block for management of abdominal pain after transarterial embolization using drug-eluting beads loaded with irinotecan.  

17 Dwyer AJ.  
Time and disease: the fourth dimension of radiology.  

18 Sangro B, Inarrazaraguiz M, Bilbao JJ.  
Radioembolization for hepatocellular carcinoma.  

19 Murthy R, Kamar P, Nunez R et al.  
Yttrium-90 microsphere radioembolotherapy of hepatic metastatic neuroendocrine carcinomas after hepatic arterial embolization.  

20 Sangro B, Carpanese L, Cianni R et al.  

21 Hoffmann RT, Jakobs TF, Kubisch CH et al.  
Radiofrequency ablation after selective internal radiation therapy with yttrium90 microspheres in metastatic liver disease – is it feasible?  

22 Cameron WB.  
*Formal Sociology, a Casual Introduction to Sociological Thinking.*  

23 Sackett DL, Wennberg JE.  
Choosing the best research design for each question.  
*BMJ* 315(7123), 1636 (1997).

24 Bolondi L, Burroughs A, Dufour JF et al.  
Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions.  

25 Mazzaferrro V, Llovet JM, Miceli R et al.  
Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis.  

26 Yao FY, Ferrell L, Bass NM et al.  
Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival.  

27 Giuliani J, Marzola M.  
Multidisciplinary approach as the key factor in the management of liver metastases from colorectal cancer.  

28 Shaya FT, Breunig JM, Seal B, Mullins CD, Chirikov VV, Hanna N.  
Comparative and cost effectiveness of treatment modalities for hepatocellular carcinoma in SEER–Medicare.  

29 Ray CE Jr, Bartaglia C, Libby AM, Prochazka A, Xu S, Funaki B.  
Interventional radiologic treatment of hepatocellular carcinoma – a cost analysis from the payer perspective.  

30 Abbott DE, Sohn VY, Hanseman D, Curley SA.  
Cost–effectiveness of simultaneous resection and RFA versus 2-stage hepatectomy for bilobar colorectal liver metastases.  

31 Abbott DE, Cantor SR, Hu CY et al.  
Optimizing clinical and economic outcomes of surgical therapy for patients with colorectal cancer and synchronous liver metastases.  

32 Cucchielli A, Piscaglia F, Creson M et al.  
Cost–effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma.  

33 Oncology Clinical Trials Office (OCTO).  
www.octo-oxford.org.uk

34 NICE.  
Interventional procedure guidance 401: selective internal radiation therapy for non-resectable colorectal metastases in the liver.  
www.nice.org.uk

35 Tanis E, Nordlinger B, Mauer M et al.  
Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases.  
Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983.  

36 Starlinger P, Alidzanovic L, Schauer D et al.  
Neoadjuvant bevacizumab persistently inactivates VEGF at the time of surgery despite preoperative cessation.  
AUTHOR GUIDELINES

Our complete Author Guidelines are available at www.futuremedicine.com

Audience
The audience for Future Medicine titles consists of research scientists, decision-makers and a range of professionals in the scientific community.

Submission
We accept unsolicited manuscripts. If you are interested in submitting an article, or have any queries regarding article submission, please contact the Commissioning Editor directly (f.lake@futuremedicine.com). For new article proposals, the Editor will require a brief article outline and working title in the first instance. We also have an active commissioning program whereby the Editor, under the advice of the Editorial Advisory Panel, solicits articles directly for publication.

Peer review & revision
Once the manuscript has been received in-house, it will be peer-reviewed (usually 2–3 weeks). Following peer review, 2 weeks is allowed for any revisions (suggested by the referees/Editor) to be made.

In-house production
Following acceptance of the revised manuscript, it will undergo production in-house. Authors will receive proofs of the article to approve before going to print, and will be asked to sign a copyright transfer form (except in cases where this is not possible, i.e., government employees in some countries).

Article types
For a more detailed description of each article type, please view our author guidelines at: www.futuremedicine.com.

Reviews
Reviews aim to highlight recent significant advances in research, ongoing challenges and unmet needs.
Word limit: 3000 words (excluding Abstract, Executive Summary, References and Figure/Table legends). Mini-reviews are also accepted.
Required sections: (for a more detailed description of these sections go to www.futuremedicine.com):
- Practice points
- Abstract
- Conclusion
- Future perspective
- References
- Reference annotations
- Financial disclosure

Patent reviews
Patent reviews aim to highlight and critically discuss the most important, promising and recent patents granted/filed in the chosen area. Discussions should be placed within the context of the relevant wider IP landscape, exploring the impact, significance and essential content of the inventions under discussion.
Word limit: 3000 words (excluding Abstract, Practice points, References and Figure/Table legends). Mini-reviews are also accepted.

Research articles
Types accepted:
Full research article: Primary research articles must present novel science that represents a substantial advancement in the field under investigation.

Preliminary communication
Preliminary communication articles are intended for short reports of studies that present promising improvements or developments on existing areas of research. Methodology: Methodology articles should provide an overview of a new experimental or computational method, test or procedure. The method described may be either completely novel, or may offer a demonstrable improvement on an existing approach.

Word limit: 3000 words
Required sections: (for a more detailed description of these sections go to www.futuremedicine.com):
- Abstract
- Introduction
- Experimental
- Results and discussion
- Conclusions
- Future perspective
- References
- Reference annotations

Perspectives
Word limit: 3000
Perspectives should be speculative and very forward-looking, even visionary. They offer the author the opportunity to present criticism or address controversy. Authors of perspectives are encouraged to be highly opinionated. The intention is very much that these articles should represent a personal perspective. Referees will be briefed to review these articles for quality and relevance of argument only. They will not necessarily be expected to agree with the authors’ sentiments.

Special reports
Word limit: 3000
Special reports are short review-style articles that summarize a particular niche area, be it a specific technique or method.

Conference scenes
Word limit: 1500–3000
Conference scenes aim to summarize the most important research presented at a recent conference relevant to the journal’s readership.

Editorials/opinions
Word limit: 1000–2000
Editorials are short articles on issues of topical importance. We encourage our editorial writers to express their opinions, giving the author the opportunity to present criticism or address controversy. The intention is very much that the article should offer a personal perspective on a topic of recent interest. Longer Commentaries (word limit: 2000–5000) are also accepted.

Product reviews
Word limit: 1500–3000
Product reviews are short review-style articles that summarize a particular piece of equipment, software or book. They should include a description of the background, and the author’s critical perspective on the product being reviewed.

Manuscript preparation
Spacing & headings: Please use double line spacing throughout the manuscript. No more than four levels of subheading should be used to divide the text and should be clearly designated.
Abbreviations: Abbreviations should be defined on their first appearance, and in any table and figure footnotes. It is helpful if a separate list is provided of any abbreviations.
Spelling: US-preferred spelling will be used in the final publication.

Figures, tables & boxes: Future Medicine has a charge for the printing of color figures (i.e., each color page) in the print issue of the journal. We have no page charges and aim to keep our color charge to a minimum. The charge does not apply to the online version of articles, where all figures appear in color at no charge.
Copyright: If a figure, table or box has been published previously (even if you were the author), acknowledge the original source and submit written permission from the copyright holder to reproduce the material where necessary.
As the author of your manuscript, you are responsible for obtaining permissions to use material owned by others. Since the permission-seeking process can be remarkably time-consuming, it is wise to begin writing for permission as soon as possible.
Please send us photocopies of letters or forms granting you permission for the use of copyrighted material so that we can see that any special requirements with regard to wording and placement of credits are fulfilled. Keep the originals for your files. If payment is required for use of the figure, this should be covered by the author.

Key formatting points
Please ensure your paper concurs with the following article format:
Title: concise, not more than 120 characters
Author(s) names & affiliations: including full name, address, phone & fax numbers and e-mail.
Abstract: a single paragraph summarizing the invention under discussion.
References: a list of every reference cited in the text.
Figures/Tables/Boxes: Summary figures/tables/boxes are very useful, and we encourage their use in reviews/perspectives/special reports. The author should include illustrations and tables to condense and illustrate the information they wish to convey. Commentary that augments an article and could be viewed as ‘stand-alone’ should be included in a separate box. An example would be a summary of a particular trial or trial series, a case study summary or a series of terms explained.

If any of the figures or tables used in the manuscript requires permission from the original publisher, it is the author’s responsibility to obtain this. Figures must be in an editable format.