TREATMENT STRATEGIES
GASTROENTEROLOGY

Volume 1 Issue 1

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- **Gastrointestinal Tumours**
- **Liver Cancer**
- **Renal Denervation**
- **Upper Gastrointestinal Tumours**

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Current Standards and New Trends in the Primary Treatment of Colon Cancer

Minimally Invasive Surgery of Liver Neoplasms

Renal Denervation for Resistant Hypertension

Early Detection of Upper Gastrointestinal Tumours Based on Molecular Analysis of p53 Expression

Includes a review of the 20th UEG Week 2012

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Interactive Luncheon Workshops

E-posters

Industry Exhibition

Networking Breaks and Reception

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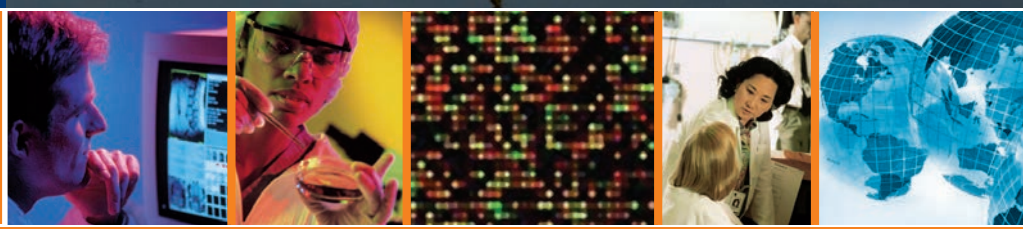
ILCA
International Liver Cancer Association



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TREATMENT STRATEGIES - GASTROENTEROLOGY

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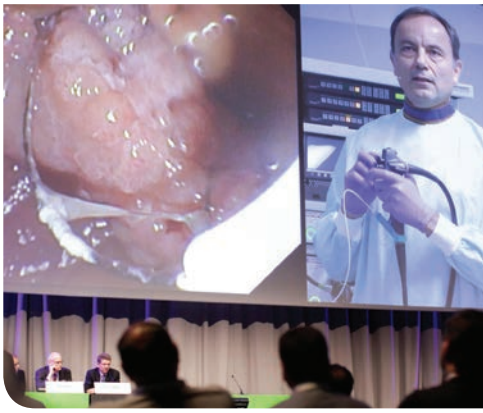
Printed by Printech (Europe) Limited



Welcome...

I am delighted to welcome you to the inaugural edition of *Treatment Strategies – Gastroenterology*. This issue will address key topical areas in gastroenterological medicine and features an exciting collection of articles from leading gastroenterology specialists. We hope that this addition to the *Treatment Strategies* series will provide you with a comprehensive review of the latest updates and advances from the gastroenterological field.

This edition includes an independent review of the United European Gastroenterology (UEG) Week 2012, which this year took place in Amsterdam, The Netherlands. Gastroenterology professionals from across the globe gathered at the Amsterdam RAI to discover the latest scientific advances, examine new technologies and connect with like-minded members on topics of interest.

The UEG is a non-profit organisation, which is combined of all of the leading European societies concerned with digestive disease. The UEG aims to improve standards of care in gastroenterology and promoting an ever greater understanding of digestive and liver disease among practitioners and the public. UEG Week is an excellent forum where the most recent research, breakthroughs, treatments and products within the field of gastroenterology can be shared. This year, over 14,000 delegates were in attendance, and over 3,000 submissions were received.

We hope that the information included in this edition will be useful for the readers and help serve as a forum in which to present the constantly evolving findings in the gastroenterological field. We hope to follow in the success of other *Treatment Strategies* series titles, and it would be much appreciated if you could provide us with your feedback; by working with your opinions we will ensure that *Treatment Strategies – Gastroenterology* becomes one of the most useful publications in the industry.

I am looking forward to joining you next year in Berlin for the 21st UEG Week.

Nigel Lloyd, Managing Director

The Cambridge Research Centre wishes to thank the following society for their assistance and involvement in this publication.

ILCA
International Liver Cancer Association

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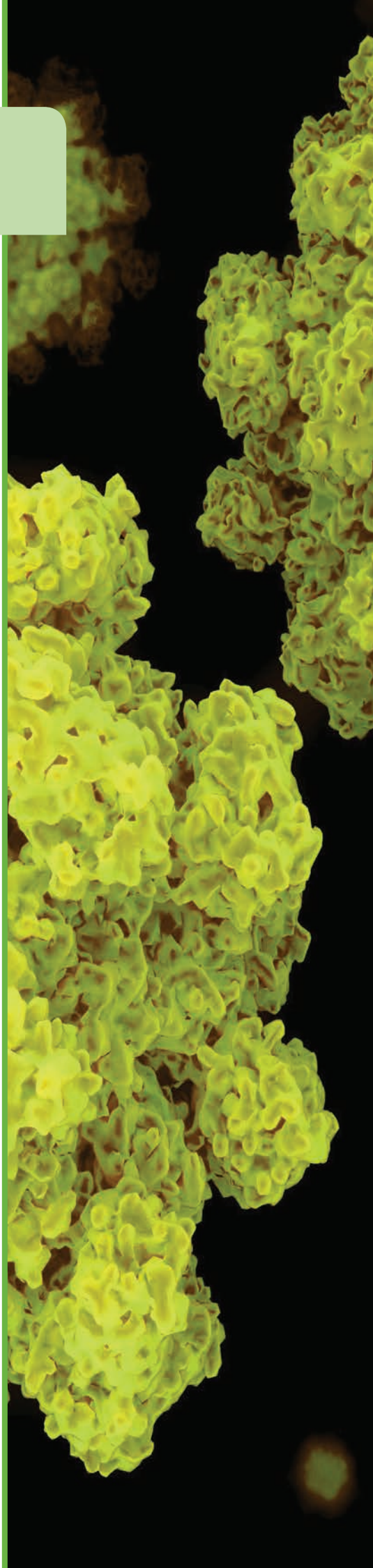

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20th UEG Week Review

20 - 24 October 2012 - Amsterdam

20th United European Gastroenterology (UEG) Week

INSIDE...

The Meeting

The Exhibition

Hannah Corby, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

United European Gastroenterology (UEG) is a professional non-profit organisation which combines all of the leading European societies concerned with digestive disease. Together, these member societies represent over 22,000 specialists working across medicine, surgery, paediatrics, GI oncology and endoscopy. UEG aims to improve standards of care in gastroenterology and promote an ever greater understanding of digestive and liver disease.

Attended by over 14,000 delegates from 125 countries, UEG Week 2012 had the best turnout in UEG's history. Including over 2,600 exhibitors and 3,400 submissions, it was an unmissable congress featuring a wealth of new research and information. This year, the congress had a number of special themes that ran over the four days, which included the modern role of multidisciplinary care and the effect of

***Introduction** continues on page 8*

The 20th UEG Week was held in the picturesque city of Amsterdam.

continued from page 7

obesity and alcohol on GI and liver disease. Additionally, the meeting featured two full days of live endoscopy, which were added in response to delegate feedback, and video case sessions featured top international experts demonstrating cutting-edge techniques in an interactive learning experience.

Indeed, there was an increased use of different formats in this year's UEG Week, including the introduction of further debate sessions and tandem talks, in which two experts present different aspects of the same problem. Interactivity was a key focus point for the congress, with both audience voting and interactive chairing being encouraged. Further sessions included clinical case studies, original research presentations, poster exhibits, workshops, seminars, symposiums and plenary lectures, as well as a postgraduate teaching programme. These sessions covered a plethora of areas within gastroenterology, from colorectal cancer therapy to endoscopy and liver disease.

The congress also hosted an international, two-day symposium entitled 'Today's Science, Tomorrow's Medicine', which focused on obesity, inflammation and carcinogenesis in the GI tract and liver. This symposium featured the best basic and translational science from around the world, and concentrated on a number of mechanisms by which excess body weight may drive carcinogenesis, and the important implications of this understanding for research and future management of obesity. There was also a free paper session, which showcased the best original research.

Additionally, the meeting also featured an ESGE Learning Area, which was open to all UEG Week delegates, and featured a variety of excellent teaching modules for endoscopy including lectures, video presentations, expert demonstrations and hands-on sessions. Coverage included procedures such as hemostatic techniques, advanced GI endoscopy, radiofrequency ablation techniques and laparoscopic and endoscopic simulator training. The learning area also featured the ESGE Lecture Theatre, which provided the opportunity to become involved in lively discussions on current hot topics.

The meeting was also a celebration of UEG Week's 20th Anniversary, and a range of exciting events were held. These events included a UEG film presentation on the history of United European Gastroenterology, a showcase of UEG's history and special anniversary symposia, which explored the progress that has been made in the field of gastroenterology as well as exploring the future of this area of medical science.

This year, UEG Week was held in Amsterdam, the capital and the largest city in the Netherlands. With a population of over 820,000 people, Amsterdam is an extremely important city both financially and culturally. It is the commercial capital of the Netherlands, and as such is considered an alpha world city. Additionally, many large Dutch institutions have their headquarters located here, and seven of the world's top five hundred companies are based in the city.

Amsterdam is also one of the most popular tourist destinations in Europe and receives more than 4.63 million international visitors annually. The city's main attractions include its historic canals, the Rijksmuseum, the Van Gogh Museum, the Anne Frank House, its Red Light District as well as its famous coffee houses. Additionally the Amsterdam

Stock Exchange, the oldest stock exchange in the world, is located in the city centre, which has a rich architectural history. Amsterdam is also renowned for its vibrant and diverse nightlife.

UEG Week was held at the Amsterdam RAI, a conference centre that holds some 50 international conferences and 70 trade shows annually. The complex consists of 22 conference rooms and 11 halls, with a total floor space of 87,000m^2. The centre focuses on creating a synergy in order to create the added value of a memorable experience and success. This wealth of experience made the Amsterdam RAI the perfect venue for UEG Week 2012.

UEG Week 2012 – A Meeting of Epic Proportions

United European Gastroenterology has reported a record attendance at its 20th annual scientific meeting, the United European Gastroenterology Week (UEG Week) held in Amsterdam. More than 14,000 researchers, physicians and other health-care professionals from 125 countries participated in a broad scientific programme, with over 2,100 original scientific research papers presented.

UEG's President, Professor Colm O'Morain, believes the secret of the meeting's success lay in both the quality of the scientific research and the emphasis on interactivity built into the programme:

"If there is one scientific congress you should attend each year if you are interested in digestive disorders, it's this one," he says. "Every year, the meeting brings together a powerful mix of scientists working hard to unravel the causes of these conditions and the specialists who diagnose and treat them. Between them, very real progress is being made."

This year's 20th anniversary of UEG Week was the most ambitious meeting yet, setting a new benchmark for the next 20 years. The programme covered a vast spectrum of topics and included plenary sessions for presentation of free papers and late-breaking abstracts, interactive keypad sessions, live endoscopy and video case studies, state-of-the-art lectures, basic science workshops, symposia, postgraduate teaching sessions and a full press programme. As well as awarding its coveted annual Research Prize, UEG also awarded140 travel grants to enable basic scientists to attend UEG Week 2012. Five top abstracts, daily 'Top Poster' prizes and eight Rising Stars were also nominated at this year's meeting.

UEG Lifetime Achievement Award

The UEG Lifetime Achievement Award recognises outstanding individuals whose pioneering and inventiveness throughout their careers have improved the Federation and inspired others. Recipients of the UEG Lifetime Achievement Award have proven lifelong excellence and leadership in the field.

Professor Galmiche contributed greatly to the development of gastroenterology nationally and internationally. His activity was characterised by a continuous and remarkable investment in favour of European gastroenterology.

Professor Galmiche's research was focused on GORD, nutrition and endoscopic technologies. He participated actively to the development of UEG, especially as a member of the Scientific Committee and as the Director of Post-Graduate Courses.

UEG Research Prize 2012

This year's prestigious UEG Research Prize of €100,000 was awarded at UEG Week to Professor Ludvig M. Sollid from the University of Oslo and Oslo University Hospital in Norway. The prize was presented in recognition of the quality and potential impact of Professor Sollid's pioneering research into the pathogenesis of coeliac disease.

Coeliac disease is a common autoimmune-like disease that causes inflammation and destruction of the lining of the small intestine. People with coeliac disease have an inappropriate immune response to cereal gluten proteins of wheat, barley and rye. This leads to chronic inflammation and damage to the wall of the small intestine that, in some people, causes severe gastrointestinal symptoms and malabsorption of vital nutrients. This can eventually result in nutritional deficiencies, anaemia, weight loss, tiredness and weakness.

Professor Sollid and his team have been investigating why some genetically predisposed individuals mount this inappropriate immune response to gluten proteins. Professor Sollid and his co-workers contributed to the discovery that the human leukocyte antigens (HLA) DQ2 and DQ8 are predisposing to coeliac disease. His group also unravelled the mechanism by which they do so, and further discovered that the enzyme transglutaminase 2, which normally is involved in the making of connective tissue, uses gluten peptides as substrates and modifies them. After the transglutaminase 2-mediated modification, gluten peptides bind better to HLA-DQ2 and HLA-DQ8. The immune system of the coeliac disease patients will respond stronger to these peptides. Strikingly, transglutaminase 2 is also the target of autoantibodies in coeliac disease.

'Through our current research with recombinant monoclonal antibodies which are made from single plasma cells of coeliac gut lesions and which are specific to transglutaminase 2 or gluten, we are hoping to understand more about the formation of the disease-related antibodies. Furthermore, we hope we can improve the serological assays used in the diagnostic work-up of coeliac disease. The UEG Research Prize will support our work in these areas."

Professor Ludvig M. Sollid

Winners of the Top Abstract Prize 2012

Bartels Sanne, The Netherlands
OP002: Inclusional Hernias and Adhesion Related Complications - Long Term Follow-up of a Randomized Trial Comparing Lapatoscopic with Open Colon Resection Within a Fast Track Program (LAFA Study)

Bernink Jochem, The Netherlands
OP398: Characterization of Novel Human Inate Lymphoid Cell Subset in Health and Disease

Chamaillard Mathias, France
OP001: NOD2-dependent Licensing of the Microbiota Intrinsically Prevents Transmissable Colitis-Associated

Ness-Jensen Eivind, Norway
OP003: Decreased Gastroesophageal Refluc Symptoms After Tobacco Smoking Cessation in a Prospective Population-based Cohort Study: The Hunt Study

Sekiguchi Masau, Japan
OP444: Favorable Long-term Clinical Outcomes of Endoscopic Submucosal Dissection for Locally Recurrent Early Gastric Cancer Follwing Non-curative Endoscopic Resection

Linaclotide Receives Positive CHMP Opinion for the Treatment of IBS-C

Almirall, S.A. and Ironwood Pharmaceuticals, Inc. have announced that the European Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion recommending the marketing approval for Constella® (linaclotide 290 micrograms), for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

The CHMP positive opinion is a recommendation to the European Commission (EC) and one of the final steps in the review of a marketing authorisation application. The EC usually follows the recommendations of the CHMP. Once approved, it will be marketed under the brand name Constella®.

"Patients with IBS-C suffer from several very uncomfortable gastrointestinal symptoms for which there are currently very few available therapies", said Bertil Lindmark, Chief Scientific Officer at Almirall, one of UEG Week's key sponsors. "With linaclotide physicians will have one of the first specifically designed therapies with proven efficacy and tolerability over time. Therefore, we are very pleased at Almirall with this first IBS-C treatment recommended for approval by CHMP and are confident in linaclotide's benefits".

This positive recommendation is based on the efficacy and safety of linaclotide evaluated in two double-blind, placebo-controlled Phase III clinical studies. The clinical trials involved approximately 1,600 adult patients, of which more than 800 were treated with linaclotide 290 mcg. In both trials, treatment with linaclotide resulted in statistically significant improvements in both abdominal pain/discomfort and degree of relief of IBS-C symptoms (co-primary endpoints), as well as complete spontaneous bowel movement frequency, stool consistency and severity of straining and bloating (secondary endpoints). These improvements were maintained over the entire treatment period (12 and 26 weeks). The incidence of adverse events was similar in both studies, with diarrhoea being the most common adverse event in linaclotide-treated patients.[1, 2]

"This positive opinion is a significant step toward helping these highly symptomatic adult patients; many of whom are searching for new treatment options," said Mark Currie, PhD, Senior Vice President, R&D and Chief Scientific Officer of Ironwood. "The discovery of linaclotide by Ironwood scientists and the work we have done to reach patients in Europe with our partner, Almirall, has been a collaborative effort with the goal of helping this underserved patient population."

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2. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009; 104 Suppl 1:S1-35

Celebrating 20 Years of UEG with a New Headquarters, a New Journal and Renewed Determination to Fight Colorectal Cancer in Europe

The 20th anniversary of United European Gastroenterology (UEG) represents a significant milestone in the history of the organisation. Twenty years ago almost to the day, scientists and clinicians gathered in the ancient city of Athens to take part in the First United European Gastroenterology Week, where seven major European societies came together to form the United European Gastroenterology Federation (UEGF, now UEG). Today, at the 20th UEG Week (UEG Week 2012) held in Amsterdam, the Netherlands, UEG President Professor Colm O'Morain, a gastroenterologist from Trinity College in Dublin, Ireland, told journalists that planning for the next 20 years had already begun. "UEG is very proud to celebrate its past, but looks forward with confidence to the future," he said. "The last year has witnessed major developments throughout the organisation, helping to build on our reputation as a driving force in Europe representing specialists in digestive and liver diseases. We now have a new corporate identity, a new central office in Vienna, a new UEG journal under development, and a very long list of what we want to achieve over the next 20 years."

UEG Past and Present

When UEG (then the UEGF) was founded in 1992, its main aim was to foster European co-operation in gastroenterology, primarily by organising an annual meeting where European researchers could present their work. Today, with 15 European and 41 national societies on-board, UEG's broader mission is to improve standards of care in gastroenterology and promote greater understanding of digestive and liver diseases amongst both the general public and within the medical profession. This, says Prof. O'Morain, can only be achieved by the year- round commitment of a dedicated team of volunteer officers supported by a professional secretariat.

"Although our flagship event is still undoubtedly the annual UEG Week meeting, which is now a leading congress on the international circuit, as an organisation, we are active throughout the year campaigning for better care for patients with digestive disorders," he said. "We have become increasingly successful at a political level and are proud to have influenced European affairs in terms of promoting colorectal cancer screening and a healthy lifestyle. However, we still have a very long way to go."

UEG and the Fight Against Colorectal Cancer

UEG is committed to working across the European Union (EU) to raise awareness of colorectal cancer (CRC) and encourage more countries to implement CRC screening programmes. According to Prof. O'Morain, CRC is now one of the most common cancers in the EU, with 400,000 new cases of CRC and 200,000 CRC-related deaths reported in the EU each year.

"We know that CRC is associated with environmental risk factors such as smoking, obesity, a lack of exercise and a poor diet, so it is important we help to educate the general public about how they can reduce their risk of developing this type of cancer," said Prof. O'Morain. "CRC screening programmes are another vital way of reducing the number of deaths from CRC in Europe, and we are pleased that some EU countries have now introduced CRC screening within their populations."

Prof. O'Morain expressed his disappointment over the recent failure of the European Commission to support further action to reduce the impact of CRC and other cancers of the digestive system, pointing out that only 8 of the 27 EU Member States had introduced nationwide population-based CRC screening programmes so far.

"It doesn't make any sense," he told journalists. "On the one hand, you have the European Parliament officially adopting a Written Declaration to fight colorectal cancer in the EU – supported by almost all MEPs – and on the other hand, you have the European Commission believing they have done enough already to reduce the impact of digestive cancer.
"We need the political will to succeed in providing colorectal cancer screening for everyone in Europe and we intend to do everything in our power to achieve that goal."

To learn more about UEG and its work, visit:
www.ueg.eu

New Electronic Capsule Confirms Feasibility of Remote-controlled Drug Delivery

The feasibility of delivering oral drug treatments to specific areas of the gastrointestinal (GI) tract has been confirmed by a first study in man using a new type of ingestible electronic "capsule". Findings were presented at UEG Week 2012.[1] Researchers used the new device to remotely control the delivery of a radioisotope to the small intestine, bringing the possibility of targeted oral treatments for localised GI conditions even closer. Dr. Peter van der Schaar, a gastroenterologist from the St. Antonius Hospital, Nieuwegein, in the Netherlands, who was involved in the study, said: "Guided by pH sensors in the capsule, confirmed by imaging, we were able to release the test compound into a short segment of the small intestine in nine out of 10 of our volunteers. The capsule was easy to swallow and demonstrated to be safe and well tolerated."

IntelliCap® System: A New Technology

The technology used in the study was developed collaboratively by Philips Research and Medimetrics in both the Netherlands and USA, with assistance from gastroenterology centres in the Netherlands. The IntelliCap® capsule is a compact capsule (measuring 27 x 11mm) comprising a drug reservoir, pH and temperature sensors, and a microprocessor. It incorporates an electromotor and piston designed to expel the contents of the drug reservoir when remote commands are received. The capsule communicates via a wireless transceiver to an external control unit worn by the individual.

"The real-time wireless data recorder enabled us to monitor the capsule's progress through the GI tract, providing continuous measurements of pH and temperature," explained Dr. van der Schaar. "The pH profile was especially important in determining where the capsule was within the intestine, as there are significant changes in pH from the stomach to the duodenum and from the small intestine to the colon. This helped us target the test compound delivery to a pre-specified region of the small intestine."

Success in First-in-human Study

This first-in-human study was designed to test the safety and functionality of the IntelliCap® system using a commonly-used medical radioisotope that can be visualised in the gut by nuclear imaging. Ten healthy volunteers ingested an IntelliCap® capsule containing 99mTc-pertechnetate (99Tc) in the morning of the study. They were monitored during the day, going home overnight, and returning to the study centre the following morning. Nuclear images were obtained at pre-determined timepoints. Once the capsule was confirmed to have passed the pylorus (determined by the pH changes transmitted), the capsule, via remote command, expelled its payload, delivering 75% of the total volume of the drug reservoir.

"After we released the 99Tc from the capsule, we could clearly see both the capsule and the radioisotope within the small bowel during nuclear scanning," said Dr. van der Schaar. "The capsule's pH readings correlated well with what we could visualise using nuclear imaging, demonstrating that pH monitoring is an effective way of determining the location of the capsule within the gut."

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1. van der Schaar P, Broekhuizen-de Gast H, Nijsen J, *et al*. Remotely controlled, small intestinal release of 99mTc-pertechnetate using an ingestible electronic device: the IntelliCap. Presentation at UEW Week 2012. Abstract UEGW12-4756.

Real Progress in Colorectal Cancer Screening in Europe

UEG is delighted to announce that another European country has moved one step closer to embracing population-based screening for colorectal cancer (CRC). At a workshop held in Tallinn, Estonia, agreement was reached on a potential 'road map' for a future population-based CRC screening programme, with a range of measures agreed to ensure effective implementation of high quality and cost-effective screening and a thorough scientific evaluation of programme outcomes. Speaking on behalf of UEG, Prof. Reinhold Stockbrugger, Chairman of UEG's Public Affairs Committee, said: "We are extremely pleased that Estonia has taken a lead in tackling this common but preventable cancer. We hope that this work can be used to help other European countries implement similar programmes."

Estonia: Driving CRC Screening into Eastern Europe

Estonia is taking a leading role in driving CRC screening further into Eastern Europe. The country has witnessed major political and economic change over the past few decades, evolving from a Soviet republic with a centralised state-controlled healthcare system to an open-market economy with a decentralised health insurance-based system. In 2002, a moderate improvement in colorectal cancer survival rates in Estonia was reported, however, rates remained considerably lower than those achieved by more affluent European countries many years previously.[1] In 2012, 5-year survival rates of 51% for colon cancer and 38% for rectal cancer were reported, and the need for earlier diagnosis to improve CRC survival rates was highlighted.[2]

"These rates of survival are similar to those reported in many other European countries," explains Prof. Stockbrugger. "However, what sets Estonia apart from some other members of the EU is that it has the passion for change, with both public health authorities and the medical specialists involved committed to starting CRC screening activities. It was therefore an honour for UEG to be invited by Prof. Heidi-Ingrid Maaroos (Estonian member of UEG's Public Affairs Committee) and Prof. Riina Salupere (President of the Estonian Society of Gastroenterology) to participate in the Tallinn workshop."

CRC Screening in Europe: Current Status

Estonia is one of the nine out of 27 EU countries that currently have no official CRC screening programme. Of the remaining 18 countries, nine have population-based programmes, seven have opportunistic programmes and two are busy with pilot studies. New member states are some of those that are lagging behind, primarily because of financial constraints and a lack of awareness amongst the general population.

"UEG is committed to working with any and every EU member state to help bridge this gap, so we can achieve the targets set out in 2010 in the Written Declaration on fighting colorectal cancer in the EU," says Prof. Stockbrugger. "We want to do this in a collaboration between UEG and its National Societies, and we have set up a committee under the chairmanship of Prof. Mark Hull from Leeds in the UK to drive this forward."

The Estonian 'road map'

The Estonian 'road map' for a future CRC screening programme was developed through extensive discussions between participants at the Tallinn workshop. It includes an agreement to immediately start 'round table' planning meetings with a view to initiating a pilot study in a limited area with good endoscopy and communication facilities. Estonia's aim is to implement population-based screening with the faecal occult blood test. The road map also contains a plan to expand colonoscopy training – including the possibility of employing nurse practitioners – and the certification of endoscopists, as set out in European quality assurance guidelines.[3] Limited opportunistic screening facilities – funded by the national insurance system – will also be set up in order to meet anticipated increased demand ahead of the establishment of a full screening programme.

"One really important aspect of the Estonian road map is that it contains plans for data registration and scientific evaluation from the very start of the programme," says Prof. Stockbrugger. "This will provide evidence for the cost-effectiveness of this new activity, which we hope will encourage other candidate countries to start CRC screening."

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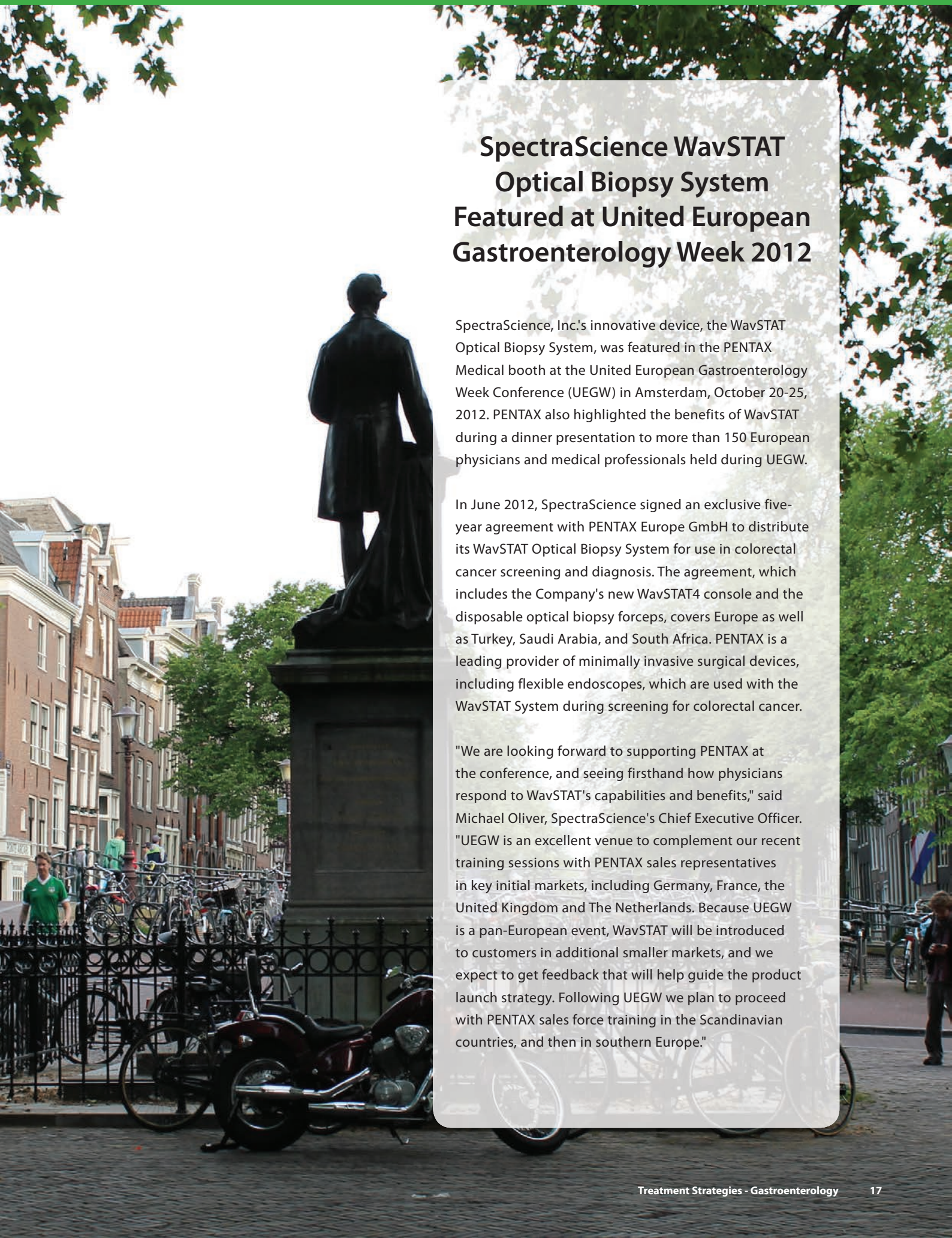

SpectraScience WavSTAT Optical Biopsy System Featured at United European Gastroenterology Week 2012

SpectraScience, Inc.'s innovative device, the WavSTAT Optical Biopsy System, was featured in the PENTAX Medical booth at the United European Gastroenterology Week Conference (UEGW) in Amsterdam, October 20-25, 2012. PENTAX also highlighted the benefits of WavSTAT during a dinner presentation to more than 150 European physicians and medical professionals held during UEGW.

In June 2012, SpectraScience signed an exclusive five-year agreement with PENTAX Europe GmbH to distribute its WavSTAT Optical Biopsy System for use in colorectal cancer screening and diagnosis. The agreement, which includes the Company's new WavSTAT4 console and the disposable optical biopsy forceps, covers Europe as well as Turkey, Saudi Arabia, and South Africa. PENTAX is a leading provider of minimally invasive surgical devices, including flexible endoscopes, which are used with the WavSTAT System during screening for colorectal cancer.

"We are looking forward to supporting PENTAX at the conference, and seeing firsthand how physicians respond to WavSTAT's capabilities and benefits," said Michael Oliver, SpectraScience's Chief Executive Officer. "UEGW is an excellent venue to complement our recent training sessions with PENTAX sales representatives in key initial markets, including Germany, France, the United Kingdom and The Netherlands. Because UEGW is a pan-European event, WavSTAT will be introduced to customers in additional smaller markets, and we expect to get feedback that will help guide the product launch strategy. Following UEGW we plan to proceed with PENTAX sales force training in the Scandinavian countries, and then in southern Europe."

21st UEG Week 2013

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A Review of the Management of Colorectal Liver Metastases

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Introduction

Colorectal cancer is a significant problem worldwide and remains one of the most common causes of cancer death, particularly in developed countries.[1] The liver is the most common site of colorectal cancer metastases with synchronous hepatic metastases present in 15-25% of patients at diagnosis. In addition, up to 50% of patients will develop liver metastases (metachronous) during the course of their disease .[2-4]

Advances in systemic chemotherapy have led to an increase in the median survival for patients with metastatic colorectal cancer. Recent studies have reported median survival of 19 months with combination chemotherapy[5] and up to 24 months[6] with the addition of targeted agents. Despite these advances, the five-year overall survival rate for patients with metastatic disease remains poor. Surgical resection of liver metastases currently offers the best possibility of cure or long term disease control. A 40% five-year survival rate and 25% ten-year survival rate has been reported from the "liver met surgery registry", based on international data collected from over 10,000 resected metastases.[7] This is consistent with published data from a number of retrospective reviews reporting five-year survival rates of between 25-50%.[8-10]

Although the criteria for liver resection have expanded with advances in surgical techniques, only 15-20% of patients are suitable for resection at presentation.[11] Combination chemotherapy, with or without targeted agents and local therapies such as radiofrequency ablation, can render previously inoperable disease operable in a further proportion of patients. The reported resection rates following chemotherapy in unselected patients with metastatic disease of 5-10% are inevitably lower[6, 12] than the 30-50% reported in small phase II studies with well selected patient populations with liver-only disease.[13-16] This finding is consistent throughout the literature.

Unfortunately 70% of patients will relapse following the resection of liver metastases,[8, 17, 18] suggesting that surgery alone is not adequate for most patients, who will require a multi-disciplinary team approach with combination treatment in order to offer the best chance of cure.

At presentation, patients with liver metastases can be divided into three groups: resectable, unresectable but potentially resectable following a response to combination chemotherapy and never resectable disease. In this review we will address the rationale and supporting data for the management of each of these groups.

Resectable Liver Metastases

Liver Resection Criteria

There are no internationally accepted, standardised criteria for liver resection and varying definitions have not only led to difficulty in interpreting clinical trials but inconsistent referral rates to surgeons. However usually, contra-indications to resection include: ≥4 metastases, disease outside the liver, metastatic lymph nodes in the liver pedicle, potential resection margin <1cm, significant co-morbid disease and likelihood of incomplete resection.[19] With advances in surgical techniques the criteria in many centres have been extended. The general consensus from an expert panel on behalf of the European Colorectal Metastases Group accepted that experienced surgeons can carry out surgery including multiple resections, provided that there is sufficient remnant liver (>30%) and surgery is not high risk due to location. Other important considerations include the presence of potentially unresectable extra hepatic disease and poor tumour biology.[20] Decisions regarding resection are clearer for patients at either end of the spectrum, with the greatest difficulty in determining the optimal treatment for borderline resectable cases. The presence of extra-hepatic metastases does not automatically preclude surgery and cases of long term survival have been reported when the extra hepatic disease is also resected.[21, 22] In a series of 75 patients who underwent complete resection of their extra-hepatic metastases simultaneously with partial hepatectomy, the three- and five-year overall survival rates were 45% and 28%, respectively.[21, 22] However, this currently represents a small group of highly selected patients and the data for resection of extra-hepatic metastases are not yet robust.

As part of a phase II trial of Cetuximab in Neoadjuvant Treatment of Non-Resectable Colorectal Liver Metastases (CELIM), a central review

of each patient's resectability was performed by an expert surgeon from each of the 17 participating centres. Thirty-two percent of patients judged to be unresectable at presentation on assessment by local teams, were subsequently confirmed to be resectable by a blinded central review.[16] In the UK, a recent study showed significant variation in the rate of liver resection across cancer networks and hospitals, suggesting either inequitable access to multimodal care, or a lack of consensus regarding what constitutes resectable disease, or both.[23]

Predictive Factors

In addition to resectability criteria, several scoring systems have been developed that predict the risk of recurrence post liver resection. These include factors such as age (>60 years), size of the largest liver metastasis (>5cm), disease-free interval between primary tumour and liver metastases (<2 years), number of liver metastases (>1) and resection margin positivity.[24] In a series of 1,001 patients additional independent predictors of poor long-term outcome included a node-positive primary, disease-free interval from primary to metastases (<1 year) and carcinoembryonic antigen (CEA) level (>200ng/mL).[26] Presentation with synchronous liver metastases as opposed to a late metachronous presentation has until recently been a well defined predictor of poor prognosis.[25-27] However, a recent retrospective analysis of patients treated in the CAIRO trial[28] reported no difference in the median overall survival (OS) of patients with synchronous liver metastases and a resected primary and those with metachronous liver metastases (defined as occurring >6 months from original diagnosis).[29] A combination of resection criteria, prognostic factors and patient factors such as co-morbidities must all be considered when assessing the appropriateness of surgery.

Surgery

The volume of liver remaining and its blood supply following resection of hepatic metastases is critical to the success of liver resection. Adequate imaging pre-operatively allows calculation of the remnantvolume as well as assessment of the anatomical location of the disease and the detection of extra-hepatic disease. Patients require contrast enhanced MRI of the liver, CT of chest abdomen and pelvis and more recently, 18-flurodeoxyglucose positron emission scan (18-FDG-PET) scan. It is recognised that if a liver resection results in 25% or less of functioning liver remaining, the rates of complications and peri-operative mortality are increased.[30] New techniques have been developed to increase the functioning liver remnant (FLR) including two stage resection and the use of pre-operative portal vein embolisation (PVE). A two stage liver resection allows one lobe of the liver to be cleared of disease and following a recovery period, disease within the contralateral lobe can be resected. PVE is based on the rationale that the embolised segment will atrophy and consequently the remaining liver tissue will hypertrophy leading to an increase in FLR of up to 30%.[30] A meta-analysis of 1,088 patients who underwent PVE, reported that 85% of patients subsequently underwent attempted hepatic resection.[31] A two stage hepatectomy can be performed in combination with PVE and/or radiofrequency ablation.

The role of laparoscopic liver resection has been explored over the past decade. Initial concerns existed regarding technical difficulties including the risk of bleeding, gas embolism and doubts regarding surgical margins and no randomised controlled trial has compared laparoscopic liver resection with open liver resection. Currently, laparoscopic liver resection remains challenging surgery and should be only be performed in selected patients by expert surgeons working in specialised centres.[32]

Adjuvant Chemotherapy

The rationale for adjuvant chemotherapy is based upon high rates of both hepatic and extra-hepatic recurrence that occur post resection.[17,18]

Several retrospective series have shown benefit for adjuvant treatment after liver resection, mostly utilising 5-flurouracil (5FU) based regimens (Table 1). Unfortunately, there have been few

First Author and Year of Publication	Number of Patients	Treatment	DFS (%)		P value	Overall Survival (%)	Hazard Ratio (HR)	P Value
			%	HR				
Langer 2002*[74]	107	5FU/LV vs. Surgery	45 35	NR	0.35	57 47	NR	0.39
Portier 2006**[75]	171	5FU/LV vs. Surgery	33.5 26.7	0.66	0.028	51.1 41.1	0.73	0.13
Ychou 2009***[76]	306	FOLFIRI + Surgery 5FU/LV + Surgery	51 46	0.89	0.44	72.7 71.6	1.09	0.69

Table 1. Randomised trials of adjuvant chemotherapy for patients with resected liver metastases.

** Langer reported 4 year DFS/OS, trial closed early due to poor accrual ** Portier reported 5 year DFS/OS *** Ychou reported 2 year DFS and 3 year OS NR=not reported*

First Author and Year of Publication	Number of Patients	Time Frame	Patients Receiving Chemotherapy (%)	Chemotherapy	HR Survival (95% CI)	P Value
Parks 2007[77]	792	1990-1998	34	5FU based	0.75 (NR)	0.007
Figueras 2007[78]	501	1990-2004	64	5FU based	0.54 (0.39-0.75)	0.0002
Wang 2007[79]	906	1991-2003	48 8	5FU based HAI (FUDR) + 5FU	0.62* (0.50-0.78) 0.51* (0.28-0.90)	<0.01 0.04

Table 2. Results of retrospective series of adjuvant chemotherapy for patients with resected liver metastases.
Abbreviations; HAI=hepatic arterial infusion; FUDR= floxuridine; 5FU=5-flurouracil; HR=hazard ratio
**benefit seen in synchronous group but not metachronous group*

randomised clinical trials of adjuvant chemotherapy, several closing early due to either poor accrual rates or inadequate power (Table 2). A combined analysis of two randomised trials of adjuvant chemotherapy with 5FU and folinic acid (FA) reported a non-significant trend towards improved median progression free survival (PFS) and OS with adjuvant chemotherapy over surgery alone of 28 vs. 19 months and OS 62 vs. 47 months respectively.[33]

Standard chemotherapy regimes for metastatic colorectal cancer now include the addition of oxaliplatin or irinotecan to fluoropyrimidine backbone. The combination of oxaliplatin with 5FU and FA (FOLFOX) has become the most commonly used adjuvant regimen, largely based on adjuvant data from resected stage III disease. Of interest, consistent with adjuvant data for stage III disease where the addition of irinotecan to 5FU does not significantly improve survival,[34] a recent phase III European study (n=306) demonstrated no significant improvement in disease-free survival (DFS) or OS with the addition of irinotecan to 5FU/FA (FOLFIRI) after liver resection.[12]

Randomised studies of either bevacizumab or cetuximab with combination chemotherapy in the adjuvant setting for early disease have so far reported negative results.[35, 36] There are also currently no data to support the use of antibodies following hepatic metastatectomy, although clinical trials of cetuximab and bevacizumab are in progress.

Resectable and Unresectable but Potentially Resectable Liver Metastases

Neoadjuvant Chemotherapy

There have been very few randomised trials of neoadjuvant chemotherapy for patients with resectable liver disease. The largest study, the EORTC 40983 trial compared peri-operative FOLFOX-4 chemotherapy with resection alone. The PFS significantly improved, hazard ratio (HR) 0.73 (95% CI, 0.55–0.97; p=0.025) in resected patients assigned to chemotherapy corresponding to a 9.2% increase in the PFS at three years, although the primary endpoint of a significant improvement in PFS in the intent to treat population was not achieved.[37]

A recent meta-analysis of peri-operative chemotherapy delivered either systemically, intra-arterially or both showed a significant reduction in recurrence-free survival (RFS), HR 0.78 (95% CI, 0.65-0.95; P=0.01) for hepatic arterial infusion (HAI) and HR 0.75 (95% CI, 0.62-0.91; p=0.003) for systemic therapy. However peri-operative chemotherapy yielded no OS advantage over surgery alone HR 0.94 (95%CI, 0.8-1.10; p=0.43). No survival benefit was evident for intra-arterial chemotherapy alone, HR 1.0 (95% CI, 0.84-1.21; p=0.96) whereas the survival difference for systemic chemotherapy approached statistical significance, HR 0.74 (95% CI, 0.53-1.04; p=0.08).[38] The results of this meta-analysis must be viewed with caution as the analysis was not based on individual patient data and in many cases, was obtained from abstract data only.

For patients with initially unresectable liver metastases, a strong correlation between response rate to chemotherapy and resection rate has been described, supporting the use of neoadjuvant regimens with the highest response.[39-41] Similarly, patients with disease progression during neoadjuvant chemotherapy have significantly worse outcomes. The current strategy for initially unresectable metastases is to aim for conversion of metastases from unresectable to resectable disease by achieving a substantial tumour reduction.[52-54] There is an argument that this aggressive strategy should also be applied to patients with resectable metastases.

Neoadjuvant chemotherapy with both FOLFOX and FOLFIRI have reported increased resection rates in both retrospective series and single arm studies of patients with unresectable liver metastases (Table 3).

First Author and Year of Publication	Number of Patients	Type of Study	Chemotherapy	Overall Response Rate (%)	Resection Rate (%)	Complete Resection (%)
Oxaliplatin Based Chemotherapy						
Alberts 2005[15]	42	Phase II single arm	Oxali/5FU/LV	60	40	33
Giacchetti 1999[80]	151	Retrospective single centre series	Oxali/5FU/LV	59	51	38
Bismuth 1996[81]	330	Retrospective single centre series	Oxali/5FU/LV	NR	16	14
Adam 2001[10]	701	Retrospective single centre series	Oxali/5FU/LV	NR	19.6	13.5
Gaspar 2003[82]	37	Retrospective single centre series	Oxali/5FU/LV	NR	27	NR
Irinotecan Based Chemotherapy						
Pozzo 2004[14]	44	Single centre prospective study	Irinotecan/5FU/LV	47.5	32.5	25

Table 3. Prospective and retrospective studies evaluating Neoadjuvant chemotherapy.
Abbreviations; Oxali=Oxaliplatin; 5FU =5 fluorouracil; LV=leucovorin

First Author and Year of Publication	Number of Patients	Chemotherapy	Response Rate (%)	Complete Resection (%)	RO Resection (%)
Delaunoit 2005[83]	795	FOLFIRI FOLFOX IROX	61 66 58	0.7 4.1 4.2	NR
Falcone 2007[46]	244	FOLFOX FOLFOZIRI	34 60	6 (12)* 15 (36)*	NR
Souglakis 2006[45]	283	FOLFOX FOLFOXIRI	33.6 43	4 10	1.4 6.5

Table 4. Phase III trials of Oxaliplatin/Irinotecan combination chemotherapy reporting liver resection rate.
Abbreviations; FOLFOX = oxaliplatin + 5FU + leucovorin, FOLFIRI = irinotecan + 5FU + leucovorin; FOLFOXIRI = oxaliplatin + irinotecan, + 5FU + leucovorin; IROX = oxaliplatin + irinotecan; OS = overall survival; NR = not reported
** % of patients undergoing complete resection who had liver-only metastases at presentation*

Oxaliplatin and capecitabine (CAPOX) is non-inferior to FOLFOX in the 1st and 2nd line treatment of advanced disease.[42, 43] In a phase II trial of 54 patients with liver metastases treated with CAPOX, an attempt at curative liver resection was undertaken in 45% of patients with initially unresectable disease and 59% in the group where upfront primary resection was considered feasible.[44]

Phase III studies have compared a triplet regimen with oxaliplatin, irinotecan and 5FU (FOLFOXIRI) to FOLFIRI with conflicting results (Table 4). One study of 283 patients failed to demonstrate superiority of the FOLFOXIRI combination.[45] However, a second study (n= 244) using higher doses of both irinotecan and oxaliplatin reported significantly higher response rates (60% vs. 34%), R0 resection rates (15% vs. 6%). Median PFS (6.9 vs. 9.8 months, HR 0.63; P <0.0006) and, median OS (16.7 vs. 22.6 months, HR 0.70; P <0.032) with FOLFOXIRI.[46]

The addition of biological agents to systemic chemotherapy improves outcome in metastatic colorectal cancer (mCRC).[47, 48] Bevacizumab increases response rates from 35% to 45% when combined with irinotecan and 5FU (IFL).[48] However, in a first line trial of bevacizumab added to oxaliplatin-based chemotherapy, whilst PFS was significantly improved with the addition of the antibody there was no significant difference in response rate. Curative liver resection was attempted in 59/700 (8.4%) of patients randomised to chemotherapy plus bevacizumab, compared to 43/701 (6.1%) randomised to chemotherapy plus placebo.[47]

Two recent single arm phase II studies of neoadjuvant CAPOX and bevacizumab in selected patients with liver-only metastases have shown high response rates. The BOXER study of 46 patients reported a response rate of 78% and 35% of patients underwent liver resection, although 20% of patients had upfront resectable disease.[49] Likewise a second single arm phase II trial of 56 patients with potentially resectable liver metastases reported objective responses in 73% of patients with

92% having undergone liver resection at the time of publication.[13]

A meta-analysis of the CRYSTAL[6] and OPUS[12] studies demonstrated that cetuximab in combination with systemic chemotherapy significantly improves response rates in K-Ras wild type mCRC.[50] A pre-planned sub-group analysis of the CRYSTAL trial reported a higher R0 liver resection rate in patients randomised to cetuximab (4.8% vs. 1.7%, p=0.002). Similarly the R0 resection rate in retrospective sub-group analysis of the OPUS study reported R0 resection rates of 9.8% vs. 4.1% in K-Ras wild type patients treated with or without cetuximab.[51]

The randomised phase II CELIM trial (n=114) evaluated the addition of cetuximab to FOLFOX or FOLFIRI in patients with initially unresectable liver-limited disease. High radiological response rates (70%) were achieved with cetuximab added to both regimens in K-Ras wild-type patients versus 41% in K-Ras mutated patients. This translated into an encouraging rate of liver resection (FOLFOX 38%, FOLFIRI 30%).[16] Based upon these data in addition to those from the OPUS and CRYSTAL studies, the UK National Institute for Clinical Excellence (NICE) has recommended the addition of cetuximab to combination chemotherapy for the treatment of patients with unresectable, liver-only K-Ras wild-type metastatic colorectal cancer.[52]

Duration of Chemotherapy

The mortality and morbidity from liver resections has fallen over recent years along with advances in surgical techniques.[37] There has been much debate over whether peri-operative chemotherapy increases the risks of surgery. Prolonged systemic chemotherapy with irinotecan could induce hepatic steatosis and steatohepatitis (yellow liver) and treatment with oxaliplatin sinusoidal congestion (blue liver), which may increase morbidity after resection but does not increase operative mortality.[53] Duration of chemotherapy is likely to be important, as morbidity in patients who received >10 cycles of chemotherapy pre-operatively was as high as 62% in one study, compared to 19% in those who received one to five cycles. In the EORTC trial of peri-operative FOLFOX, where a median of six cycles were delivered before and after surgery, only one patient was unable to undergo resection due to macroscopic liver damage.[37] An increased time interval between finishing chemotherapy and undergoing surgery is associated with reduced surgical complications and surgery is usually delayed for a minimum of four weeks following the cessation of chemotherapy.[54]

There are concerns that bevacizumab could increase surgical morbidity and mortality although there is currently little evidence to support this. The feasibility and safety of liver resection has been addressed in a number of retrospective series, none of which suggest an excess of complications with bleeding or wound healing.[55] Because of the long half-life of bevacizumab (20 days), it is commonly recommended that six to eight weeks should elapse between the administration of bevacizumab and elective hepatic resection.[56, 57] The results of a phase II study suggest that the time interval can be shortened to five weeks without an increase in operative morbidity compared to historical controls.[13]

Disappearing Metastases

Combination chemotherapy yields radiological complete response (CR) rates of 4-9% in liver metastases.[10] The optimal approach is currently unclear when liver metastases are no longer visible on pre-operative imaging and one of the major questions for the surgeons is whether the site of previously documented metastases should be resected, or left in place. In one review of 38 patients with liver metastases undergoing chemotherapy 66 metastases disappeared after treatment. However persistent macroscopic or microscopic residual disease at operation or early recurrence *in situ* were observed in 83% of metastases having a CR on imaging suggesting that in the majority of cases, resection of the sites of initial metastases is necessary. In such cases, technical problems for the surgeons at surgery remain identification of the precise site requiring resection and achievement of sufficient resection margin.[58] It has been argued that patients presenting with small synchronous metastases should be considered for upfront surgery because of the risk of chemotherapy inducing a CR, however there is currently no evidence to support this approach.

Local Therapies

Hepatic Arterial Infusion (HAI) Chemotherapy Alone

The liver has a dual blood supply and metastases >1cm in size receive their blood supply via the hepatic artery. Direct infusion of chemotherapy into the hepatic artery delivers a high drug concentration to the metastases whilst sparing normal liver tissue. There have been a number of trials of HAI, however interpretation is difficult due to the use of different drugs, schedules, and dose intensities, additionally many of the trials allowed crossover from intravenous administration to HAI. A Cochrane review concluded that the currently available evidence does not support the use of HAI alone for the treatment of patients with unresectable liver metastases.[59]

HAI and Systemic Chemotherapy

The benefit of combined systemic and intrahepatic arterial chemotherapy was evaluated in an Intergroup study that randomly assigned 109 completely resected patients to observation versus a combination of HAI with floxuridine (FUDR) and infusional 5-FU. Combined therapy was associated with significantly longer time to recurrence and overall RFS, however there was no benefit in terms of median OS.[60]

With the introduction of modern chemotherapy agents, studies have compared HAI chemotherapy and intravenous irinotecan and oxaliplatin. High response rates (90%) were seen in a phase I trial of systemic oxaliplatin combination therapy together with HAI

chemotherapy of FUDR and dexamethasone in patients with unresectable liver metastases.[60] Oxaliplatin was also administered intra-arterially together with intravenous 5-FU/FA in a French study with a response rate of 64%.[61] Similarly encouraging response rates (34.5%) were observed for triple-drug therapy delivered intra-arterially in heavily pretreated patients.[62] However, HAI is not without toxicity and routine use of HAI chemotherapy after liver resection has not gained widespread acceptance.

Trans-arterial Chemoembolisation (TACE)

TACE has been evaluated in a number of studies with various agents, including 5FU, mitomycin C and gemcitabine. In a non-randomised prospective series of 483 patients treated with mitomycin C with or without gemcitabine partial response following chemoembolisation was seen in 14.7%, stable disease in 48.2% of patients and the median survival was 14 months.[63]

A novel drug delivery system of drug eluting beads has been developed which, enables deposition of a chemotherapeutic agent into the liver without significant release into surrounding tissues. An interim report of a single arm study of 55 patients evaluating irinotecan loaded beads (DEBIRI) reported a response in 71% of patients at three months, 56% at six months and 40% at twelve months. Ten percent of patients were downstaged and of these, four were treated with surgery and two with radiofrequency ablation (RFA).[64] There are a number of ongoing studies evaluating DEBIRI in combination with systemic chemotherapy and targeted agents including a randomised European phase II testing DEBIRI plus cetuximab in K-Ras wild-type patients which is currently open to recruitment.

Selective Internal Radiation Therapy (SIRT)

SIRT uses microspheres containing the radionuclide Yttrium-90 (90Y) injected into the arterial supply of the liver using angiography. The microspheres embolise within the tumour vessels thereby enabling the local delivery of tumouricidal doses of radiation irrespective of the tumour number, size or location.

Retrospective analyses of SIRT as salvage treatment reported median survival of 10.5 months in responders and 4.5 months in non-responders.[65]

A phase III trial of protracted 5FU with or without 90Y spheres reported disease control rates of 35% in the 5FU arm and 86% in the combination arm. There was a significant difference in time to liver progression (TTLP) and time to progression (TTP), but no difference in OS. However, this may have been confounded by the crossover of 70% of the patients from the 5FU arm.[66]

In addition to the results in chemorefractory disease, small prospective studies have demonstrated the potential of combination 90Y and chemotherapy in the first and second line setting. A phase I study of SIRT with FOLFOX (n=20) showed 18 partial responses and stable disease in two patients. Median PFS was 9.3 months and median TTLP was 12.3 months and two patients underwent liver resection following treatment.[67]

The challenge remains incorporating SIRT into current treatment paradigms. In order to address this two planned randomised controlled trials are underway assessing the addition of SIRT to FOLFOX chemotherapy as first line treatment of metastatic colorectal cancer (mCRC). SIRFLOX an international multicentre trial aims to recruit 382 patients, the primary end point is PFS. FOXFIRE is a UK trial with a target of 490 patients, the primary end point is OS.

Radiofrequency Ablation (RFA)

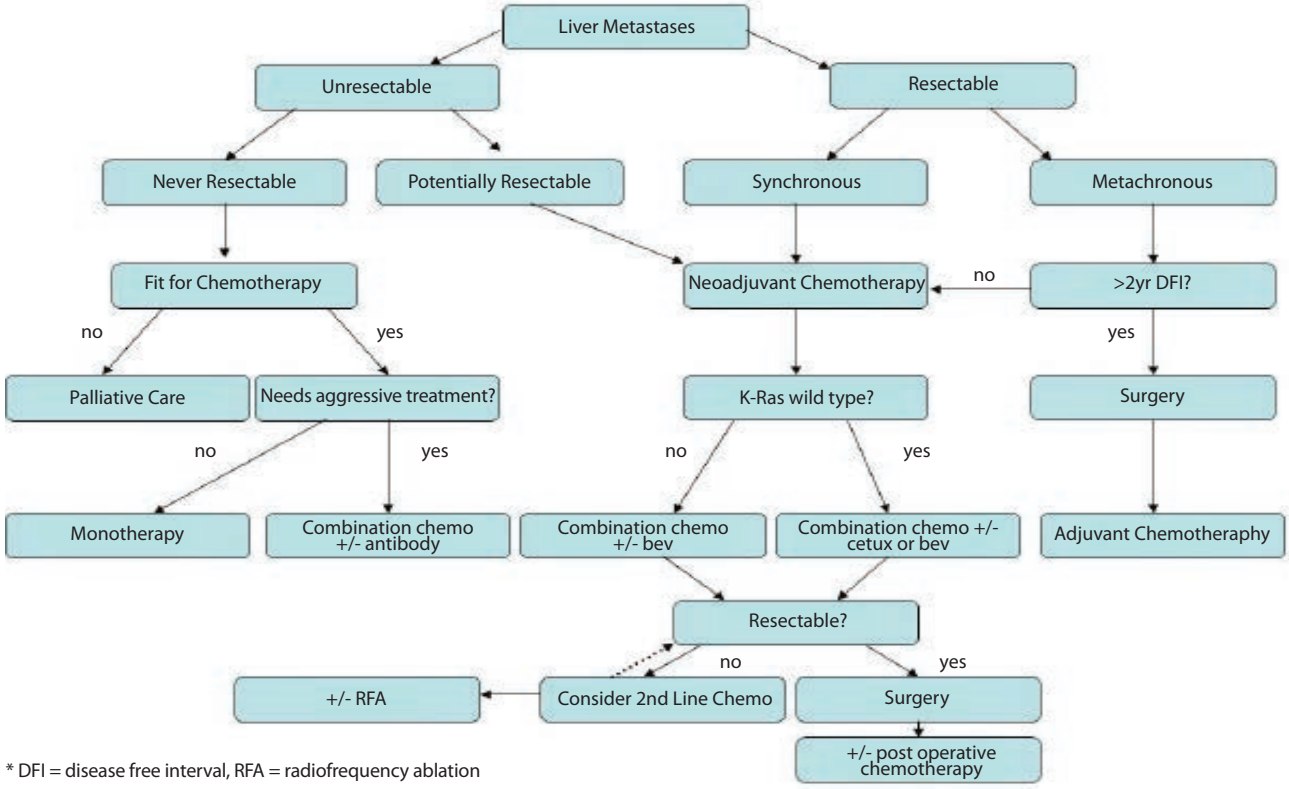
RFA destroys tumour cells locally by generation of high-frequency current, inducing cell death by heat induction. The role of RFA has been widely debated and no randomised controlled trials have compared RFA with surgery. RFA has shown variable results in non-randomised retrospective studies, with most showing inferior outcomes for RFA when compared to surgery, although this may have been confounded by patient selection.[68, 69] RFA may also be used as an adjunct to surgery and chemotherapy in selected patients with unresectable liver-only metastases.[70] The phase II CLOCC study randomised 119 patients to six months of FOLFOX (and bevacizumab from 2005) with or without RFA. The median PFS was 16.8 months in the RFA + chemotherapy arm (95% CI; 11.7-22.1) and 9.9 months (95% CI; 9.3-13.7) with chemotherapy alone (p=0.025).[71]

External Beam Radiotherapy

The liver has a low tolerance for radiotherapy and doses to the whole liver greater than 30-33Gy are associated with radiation induced liver damage.[72] Advances in radiation planning, motion management and radiation delivery using image guided radiotherapy (IGRT) have allowed higher, more conformal doses of radiotherapy to be delivered improving the probability of tumour control with less risk of toxicity. A phase I study determined the safety of six fractions of Stereotactic body radiotherapy (SBRT) up to 60Gy for patients with unresectable metastases. The 12 month tumour control was 70% and treatment was well tolerated by patients.[73] Further studies are required to evaluate this approach.

Biomarkers

Liver resection criteria, and independent predictive factors are used to determine management of patients with liver metastases. The introduction of targeted agents has increased the relevance of prognostic and predictive biomarkers in patient selection. Such biomarkers allow refinement of the sub-population to those most



* DFI = disease free interval, RFA = radiofrequency ablation

Figure 1. Treatment algorithm for colorectal liver metastases.

First Author and Year of Publication	Number of Patients	Type of Study	Chemotherapy	Overall Response Rate (%)		P Value (95% CI)	Resection Rate (%)	RO Resection Rate (%)		
				ITT	K-Ras w/t			ITT	K-Ras w/t	K-Ras Mutant
Van Cutsem 2009[6]	599	Phase III	FOLFIRI FOLFIRI + cetux-imab	38.7 46.9	43.2 59.3	0.002 (1.45 to 6.27)	3.7 7.0	1.7 4.8	NR	NR
Bokemayer 2009[12]	337	Phase III	FOLFOX FOLFOX/cetux-imab	36 46	37 61	0.64	NR	NR	4.1 9.8	12.1 1.9
Folprecht 2010[16]	114	Phase II	FOLFOX/cetux-imab FOLFIRI/cetux-imab	68 57	70*	0.23	46*	38 30	NR	NR
Saltz 2008[47]	1404	Phase III	CAPOX or FOLFOX CAPOX or FOLFOX + beva-cizumab	47 49	NA	0.31 (0.71 to 1.14)	6.1 8.4	NR	NA	NA
Wong 2009[49]	46	Phase II single arm	CAPOX + bevaci-zumab	78	NA	NR	40	NR	NA	NA
Greunberger 2008[13.84]	56	Phase II single arm	CAPOX + bevaci-zumab	73	NA	NR	NR	92	NA	NA
Cassidy[42]	1401	Phase III	FOLFOX or XELOX FOLFOX or XELOX +bevaci-zumab	NR	NA	NR	6.1 (11.6)** 8.4 (12.3)*	4.9 6.3	NA	NA

Table 5. Randomised studies of targeted agents in addition to combination chemotherapy reporting liver resection rate.
Abbreviations; FOLFOX= oxaliplatin,+ 5FU/LV; FOLFIRI=irinotecan + 5FU,/LV; NR= not reported; NA,=not applicable; ITT= intention to treat; K-Ras *w/t,=*K-Ras *wild type. * Results for both FOLFOX and FOLFIRI arm in* K-Ras *w/t. ** % of patients with liver only disease and RO resection*

likely to benefit as well as minimisation of unnecessary toxicity and cost in the setting of futility. K-Ras mutation status is the first example of a biomarker now routinely used in clinical practice to predict response to anti EGFR therapies. It is essential that current studies include tissue collection for biomarker evaluation so that future studies can select patients most likely to benefit from these agents.

Never Resectable Liver Metastases

The majority of patients with liver metastases are unlikely to ever be cured. Decisions regarding the intensity of systemic chemotherapy should be determined by the aim of treatment; prolongation of survival, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life.

The importance of palliative care should not be overlooked in this group of patients who despite advances in treatment still have a relatively poor prognosis.

Conclusions

Surgical resection of liver metastases in combination with systemic chemotherapy offers patients the best chance of cure. In order to achieve maximal tumour response and resection rates, combination chemotherapy with or without a monoclonal antibody is a standard practice in the neoadjuvant treatment of both resectable and unresectable liver-only disease. Current randomised clinical trials further intensifying systemic chemotherapy with combinations of FOLFOXIRI and/or the addition of monoclonal antibodies are underway.

Patients with unresectable liver-only disease at presentation should be re-evaluated every two to three months whilst on treatment to assess potential conversion to resectable disease. If the disease becomes resectable, three to six months of adjuvant treatment should follow surgery with a regimen determined by the duration and response to peri-operative treatment. There may be a role for upfront surgery in those patients presenting with small resectable metachronous liver metastases following a prolonged disease free interval (>2 years), however if no peri-operative chemotherapy can be or has been administered, post-operative adjuvant treatment would usually be considered.

Given the debate over potential liver toxicity with peri-operative chemotherapy, the total duration of chemotherapy should be limited to a maximum of six months where possible. Surgery should be delayed for at least four weeks after chemotherapy to minimise morbidity and patients who have received bevacizumab in combination with chemotherapy should wait a minimum of five weeks before undergoing surgical resection.

In patients with unresectable disease, localised therapies such as RFA may be a useful adjunct to chemotherapy and possibly surgery in selected patients treated at specialist centres. The role for other localised therapies such as SIRT and TACE with DEBIRI, in combination with systemic chemotherapy is under evaluation.

Acknowledgements

The Authors are supported by National Health Service funds given to the National Institute for Health Research Biomedical Research Centre, UK.

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Combination of Surgery and Tryrosine Kinase Inhibition for Gastrointestinal Stromal Tumour

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Introduction

The promise of improved cancer therapeutics that eminiate from pre-clinical studies elucidating the molecular pathogenesis of malignant proliferation has been a long-time goal of cancer research. A classic example of the methodology can be found in the management of Gastrointestinal Stromal Tumour (GIST). Within the past decade, this previously obscure mesechymal tumour has undergone a dramatic change in clinical management, particularly in consideration for treating recurrent/metastatic disease. The pathobiology of GIST is defined by the presence of the mutated receptor tyrosine kinase KIT. This mutated protein contributes to an autonomous proliferative state and was found in over 80% of GIST specimens with a much smaller percent displaying a mutually exclusive mutation in another structurally similar transmembrane kinase, platelet derived growth factor receptor-alpha (PDGFR).[1-4] Importantly, Imatinib Mesylate (Gleevec®) (IM) a small molecule inhibitor of both KIT and PDGFR was proven in pre-clinical evaluations and clinical trials to provide a targeted effect on GIST cell growth.[4, 5] Well-populated clinical studies with long-term follow-up have solidified the benefit of IM in the treatment of metastatic or recurrent GIST, a malignancy previously known to be refractory to systemic therapy.[6, 7]

In a metastatic malignancy that historically had a reported median survival of 12 to 18 months, the benefit of tyrosine kinase inhibition (TKI) resulted in a median time to progression of 24 months and a median overall survival of 57 months.[5] The proven benefit of IM in the management of metastatic GIST resulted in a successful Phase III randomised clinical trial of post-operative adjuvant IM vs. placebo for intermediate to high risk primary GIST. This study published in 2009 suggested a Relapse Free Survival (RFS) benefit of adjuvant IM given for one year after complete surgical resection.[8] The paradigm of combination targeted TKI and surgical resection is presently the subject of clinical investigations. Data is being compiled for this combination addressing its efficiency in both an adjuvant and neoadjuvant setting as well as evaluating optimal duration of therapy. This information will be important going forward not only for GIST but maybe applicable for other solid tumours as well, as more effective molecularly targeted therapies emerge. This review will provide an update on the evolving role of surgery, treatment with TKI therapy, and their combination in the management of GIST.

Surgery in the Pre-TKI Era

Historically in the pre-TKI era surgery was the only effective treatment for GIST. Surgical resection remains the mainstay of management of primary GIST and those standard surgical principles are applicable now even with the advent of TKI therapy. These principles are consistent with the biology of these mesenchymal malignancies: complete surgical resection to microscopic negative margins, no indication for formal lymphadenectomy, and careful handling of the tumour to avoid mechanical rupture and implantation. Retrospective reviews however provide evidence that even after ideal gross and microscopic margins recurrence rates after resection of primary or selected metastatic GIST can approach 80% in long-term follow-up.[9]

Recurrence Risk Factors

Knowledge of risk factors for recurrent GIST after successful surgical resection is a critical factor in recommending adjuvant TKI therapy. The majority of GIST recurrence typically occur in the abdomen which then spreads to the liver and peritoneal surfaces. These recurrences are often multiple precluding surgical resection. The majority of the variables linked to recurrence risk are based on retrospective data and are related to a variety of surgical, tumour, and pathologic factors. These factors include completeness of surgical resection, tumour size, mitotic count, tumour site, and c-kit mutational status.[10-12] The mitotic count is a surrogate for tumour

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grade and the mutational status, although not as definitive a marker of risk seems to correlate Exon 11 mutation to enhanced risk of recurrence. The GIST risk classification scheme proposed by Miettinen and Lasota of the Armed Forces Institute of Pathology is the most accepted review for recurrence determination. This is a retrospective study based on long-term follow-up data from over 1,900 GIST patients. Risk is stratified according to tumour size, number of mitoses per 50 high-powered fields and tumour location.[13] In this classification non-gastric GIST location seems to portend a worse prognosis and risk is subdivided into low, intermediate, and high recurrence potential (Figure 1). In addition to this risk classification scheme there have been other proposed risk calculators such as the nomogram featured in a recent publication by Gold *et al.* that have proven useful in discussing the pathology with the patient after primary GIST resection particularly with relevance to adjuvant therapy recommendations.[14]

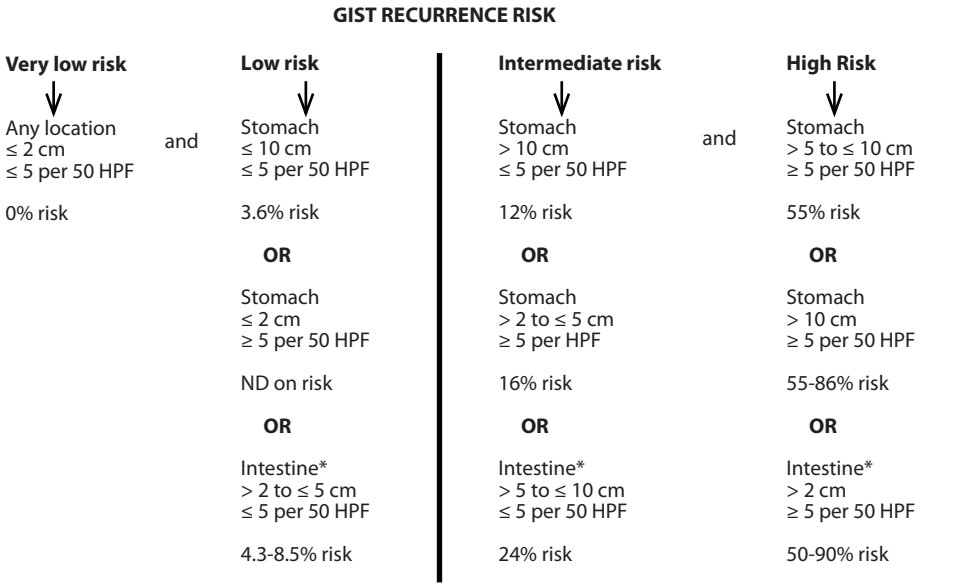

Figure 1. Recurrence risk stratification after surgical resection.
*Intestine denotes duodenum, jejunum/ileum or rectum.

Combination of Surgery and TKI for Metastatic GIST

Experience with IM in metastatic GIST suggests that the majority of patients will achieve a response within 6 months and have a 24 month median interval to disease progression.[15] From this information it would seem that any potential salvage for surgical intervention in resectable GIST should be entertained within a 12-18 month time frame after intiation of IM therapy. In patients with IM responsive or long-term stable metastatic GIST, surgical resection in selected patients can be considered to possibly enhance disease control and potentially obviate future drug resistance. Anecdotal reports and retrospective series of patients with metastatic GIST have evaluated the possibility of complete resection of metastatic disease.[16-18] The conclusion of these studies consistently emphasise that those patients with partial disease response to IM have a much higher rate of complete tumour resection than those patients with non-responding and progressive disease. Although it is certainly an open question as to what extent surgical intervention can improve RFS or overall survival (OS) in patients with metastatic GIST responding to TKI therapy, there is potential that long-term favourable disease outcome may correlate with the disease status at the time of surgical intervention. Retrospective series evaluating an end-point of RFS suggests that those patients who achieved stable disease or limited focal progression on TKI therapy compared with those who had generalised disease progression were more likely to have sustained RFS following surgery. In a series published by Raut the post-operative outcome of 69 patients with metastatic disease indicated 78% with stable disease on TKI and 25% with limited progression before surgery showed continued RFS compared with only 7% with generalised progression on TKI prior to surgery.[17] Sym *et al.* noted similar findings in their series with a median follow-up of 25 months, median PFS was 27 months in the group with responsive disease vs. 3 months in the group with generalised progression.

This concept of surgical intervention after TKI for metastatic disease is far from an established recommendation based on these limited and highly selective patient series. It is also important to note that the continued use of TKI therapy after successful surgery for metastatic disease is critical for disease management. The question of surgical intervention in this clinical setting was proposed in a Phase III study by the EORTC-STBSG where patients with metastatic GIST were randomised after 6-12 months responding to IM therapy to surgical intervention and continued drug or just continued drug without surgery. Unfortunately this trial was suspended due to accrual issues.

TKI as a Surgical Adjuvant

The noted success of IM in the metastatic setting, the drug's manageable toxicity, and the high reported recurrence rate after resection of primary GIST, stimulated investigation into adjuvant use of IM. The most influential trial to date to evaluate adjuvant IM was reported by the American College of Surgeons Oncology Group (ACOSOG) and consisted of a randomised Phase III trial design using either IM or placebo for a 12 month interval after complete resection of intermediate to high-risk primary GIST (defined as ≥3cm, did not stratify for mitotic rate or tumour location). During the post-op treatment year there was a 17% recurrence rate in the placebo group vs. a 2% recurrence rate in the IM group. There was, however, no survival advantage due to the cross-over design of the

trial. Based on the favourable results for RFS, 400mg/day adjuvant IM for primary GIST ≥3cm received FDA approval in 2008.[8] Long-term follow-up results are awaited. Results of KIT mutational analysis from the trial were recently presented. GIST with Exon 11 mutations were significantly less likely to recur by two years when treated with IM as were GIST with PDGFR mutations. However, wild type GIST (no KIT or PDGFR mutation) did not appear to benefit from adjuvant IM.

The duration of adjuvant therapy remains controversial. Although the ACOSOG trial established one year as a standard, it is apparent that the incidence of recurrence increases dramatically after drug cessation, particularly for GIST ≥10cm. The FDA approval did not include a specific duration of adjuvant drug exposure. Based on estimated recurrence risk (Figure 1) it seems likely that a duration of therapy greater than one year may be necessary for full benefit in those GIST patients at intermediate to high risk. In addition, the ACOSOG study did not stratify for mitotic rate which may be an important variable to consider in the duration of therapy discussion. Several clinical studies are presently awaiting data maturation and analysis regarding efficacy of therapy duration. Two studies from Europe comparing one vs. three years and two years vs. observation will include mitotic rate as a stratification variable. Recently a five year adjuvant IM Phase II trial was completed in the US. Results of these trials will likely modify adjuvant indications in the future.

Neoadjuvant IM for Primary GIST

Based on recommendations from both European and US guidelines the use of pre-operative IM in the management of primary GIST may be considered. This consideration is usually better suited for patients where an RO resection may be difficult to achieve or may be less morbid if tumour cytoreduction was possible. In addition, particularly for large tumours where vascularity and friability could lead to mechanical rupture, pre-operative IM may reduce this risk. There is obvious advantage in terms of expected surgical morbidity avoidance when GIST in certain anatomic sites, such as GE junction, duodeneum, or rectum can be downstaged to facilitate their removal. These considerations have yet to be tested in large prospective trials. The only prospective multi-institutional neoadjuvant GIST trial reported to date was RTOG 0132.[20] This trial established the safety profile of pre-operative IM and the potential for successful tumour downstaging of primary GIST. Several retrospective studies utilising neoadjuvant IM for primary GIST have also supported this concept of tumour downstaging prior to consolidation surgical resection.[21-23] It is important to note that in the setting of primary GIST that surgical resection be offered early on and considered between 3 to 9 months to avoid potential tumour progression. In addition, adjuvant therapy should be continued post-operatively for appropriate patients. The indications for neoadjuvant therapy have not been clearly defined at this time and careful consideration for the particular clinical situation is necessary to determine the optimal recommendation.

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Current Standards and New Trends in the Primary Treatment of Colon Cancer

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Introduction

Worldwide, 1.23 million patients were diagnosed with colorectal cancer (CRC) in 2008 accounting for 9.7% of the total cancer burden after lung (1.61 million) and breast cancer (1.38 million).[1] In Europe CRC is the most common cancer (13.6%) and was responsible for 212,000 deaths in 2008, thus representing the second most common cause of cancer death after lung cancer.[2] Cumulative lifetime risk is about 5%. Approximately 25% of patients with CRC present with metastatic disease at time of diagnosis, and up to 40% of patients will develop metastases during their course of disease resulting in the relatively high overall mortality rate of CRC. Nevertheless, mortality from CRC has declined during the last two decades, especially in northern and western Europe, potentially related to improved detection (screening and early diagnosis) and advances in adjuvant treatment.[3]

In the last 15 years, significant progress in the management of CRC has been achieved with several new agents licensed extending median overall survival for stage IV disease to about two years. Treatment of CRC is stage-specific and multidisciplinary incorporating surgeons, medical and radiation oncologists, as well as gastroenterologists. Therefore, management of individual patients should be discussed in a multidisciplinary team. Whereas a curative approach is being applied especially to early stages (0-III, according to Union for International Cancer Control/UICC). Patients with limited stage IV disease (liver and/or lung or peritoneal metastases) might still be curable by multidisciplinary management combining surgery, perioperative chemotherapy and/or radiotherapy.

Early Colon Cancer

Despite increasing availability of drugs in the metastatic setting, adjuvant treatment for stage II and III colon cancer is still based on fluoropyrimidines (FP) with or without oxaliplatin. Although the results of the last cetuximab-based trial (PETACC 8) are still pending, further development of adjuvant use of cetuximab and bevacizumab after the results of NO147, NSABP C-08, and AVANT seems unlikely.[4-6] Interestingly, FOLFIRI and cetuximab seem to be highly active in a small group of patients initially included in the NO147 trial before closing the irinotecan arms due to failure of adjuvant FP and irinotecan combination in several trials.[7-11]

Prognostic and Predictive Markers

Current research focuses on prognostic and predictive markers for tailoring treatment, particularly in stage II disease. Especially high frequency of microsatellite instability (MSI-H)/deficient DNA mismatch repair (dMMR) is intensively studied. Patients with MSI-H/dMMR tumours have a proven better prognosis.[12-14] Early analyses have furthermore suggested a detrimental effect for adjuvant treatment with 5FU in patients with stage II MSI-H/dMMR tumours. However, these findings could not be confirmed by recent analyses including larger numbers of patients (PETACC 3, QUASAR).[12, 13, 15, 16] One potential explanation for the discordance of the data might be that the patients were insufficiently analysed for germline vs. sporadic MMR defects.[14] Furthermore, gene array analyses are currently being investigated, comprising prognostic informations.[17, 18]

Timing and Duration

Adjuvant treatment should be administered as soon as possible, since survival will be relevantly impaired with every four-week delay or initiation of chemotherapy beyond eight weeks after resection.[19-21] However, despite a decreased benefit according to most recent data adjuvant treatment might still yield some benefit even if applied beyond the commonly used limit of eight weeks.[19]

At present, adjuvant treatment should be given for six months.[22] Particularly with regard to the cumulative neuropathic side effects of oxaliplatin further reduction of treatment duration is reasonable. Accordingly, shorter adjuvant treatment duration (three months) is currently under evaluation in the IDEA "trial" (International Duration Evaluation of Adjuvant chemotherapy), comprising data of 12,000 patients derived from 6 ongoing trials (data available 2014).

Treatment According to Stage

As mentioned above, stratifying patients with stage II disease into risk categories is currently under evaluation. However, to date

clinicopathological risk factors (lymph node sampling <12, poorly differentiated tumour, vascular or lymphatic or perineural invasion, obstruction or perforation or pT4 stage) are used to classify patients into high-risk (HR) and low risk (LR). HR stage II patients, defined by occurrence of at least one of the clinicopathological risk factors, should receive adjuvant chemotherapy with single-agent fluoropyrimidine.[23] Adding oxaliplatin in HR stage II patients showed a non-significant trend towards increased disease-free survival (DFS), without affecting overall survival (OS) in the MOSAIC trial.[24] More recently, a pooled analysis of NSABP C-05 to C-08 has shown a benefit adding oxaliplatin to 5FU in all stages for DFS and OS and no significant interaction between stage (II/III) or risk group within stage II (LR/HR) and oxaliplatin. Furthermore, a small, non-significant OS benefit of 2.5% for LR and 3.5% for HR was demonstrated.[25] Therefore, combination with oxaliplatin might be considered in patients with higher risk of recurrence and less than 70 years of age.[26] Patients with stage II disease without risk factors might still be treated with adjuvant FP.[23, 27] MSI/MMR might help in determining the patients' prognosis and thus assessing the potential benefit of adjuvant treatment.

Adjuvant treatment with a combination of FP and oxaliplatin (FOLFOX, XELOX) should be offered to all eligible patients with stage III disease.[28, 29] Single-agent FP is an option if oxaliplatin has to be avoided. Particularly, physically fit patients older than 70 years (biological age) with stage III disease should receive adjuvant chemotherapy with single-agent FP.[27, 30]

Metastatic Colon Cancer

Prognostic and Predictive Markers

KRAS mutation, which excludes patients from treatment with anti-EGFR antibodies, is the only relevant predictive molecular marker for treatment decision at the moment.[31] Some concerns were currently raised about KRAS codon G13D mutation (5% of patients), which seem not to preclude efficacy of anti-EGFR treatment in KRAS mutant patients.[32, 33] However, data are conflicting and no definite conclusion can be drawn at the moment.[34] Despite the strong adverse prognostic effect of BRAF mutation (8% of KRAS wild-type patients), the predictive value for treatment with anti-EGFR antibodies is still unclear, with some analysis indicating lack of benefit,[34-37] whereas others like CRYSTAL/OPUS or CAIRO 2 suggest either some benefit or similar prognosis independent of cetuximab treatment.[38, 39]

Selection of Treatment

The selection of first-line treatment is dependent on the clinical presentation, tumour biology, patient characteristics, and drug-related factors. As shown in table one, patients can be stratified into four groups with different treatment aims and intensity.[40]

Patients presenting with resectable liver and/or lung metastases (group A) should undergo resection and/or multimodal management in order to decrease recurrence rates. Post- and/or preoperative systemic chemotherapy with FP and/or oxaliplatin shows a trend towards a benefit regarding progression-free (PFS) and OS, without increasing postoperative complication rates.[41, 42] Since all available trials failed to show a statistically significant improvement, no broadly accepted standard treatment exists. Currently ongoing trials evaluate the addition of further agents, e.g. cetuximab, bevacizumab and/or irinotecan to perioperative FP and oxaliplatin.

Achievement of a disease-free or no evidence of disease (NED) status after chemotherapy, surgery and/or locally ablative techniques (e.g. radiofrequency ablation) offers the potential of long-term survival or cure in an otherwise palliative situation. While this applies particularly to liver and lung metastases, it might also be the case for limited

Group	Clinical Presentation	Treatment Aim	Treatment Intensity
A	clearly R0-resectable liver and/or lung metastases	• cure, decrease risk of relapse	nothing or moderate (FOLFOX)
B	liver and/or lung metastases only		
	• might become resectable after induction chemotherapy • ± limited/localised metastases to other sites, e.g. locoregional lymphnodes • physically able to undergo major surgery (biological age, heart/lung condition)	• maximum tumour shrinkage	upfront most active combination regimen
C	multiple metastases/sites, with		
	• rapid progression and/or • tumour-related symptoms/risk of rapid deterioration • co-morbidity allows intensive treatment • or group 3 without severe comorbidity	• clinically relevant tumour shrinkage as soon as possible • at least achieve control of progressive disease	upfront active combination: at least doublet
D	multiple metastases/sites, with		
	• never option for resection • no major symptoms or risk of rapid deterioration, or • severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1+2	• abrogation of further progression • tumour shrinkage less relevant • low toxicity most relevant	• sequential approach: start with - single agent, or - doublet with low toxicity • exceptional alternative: "watchful waiting"

Table 1. Clinical groups for first line treatment stratification (modified from 40).

peritoneal disease. The most active induction chemotherapy should be chosen for all potential NED-amenable patients (group B). Treatment regimens with highest response rates in Phase III trials are combination chemotherapy with EGFR inhibitors for KRAS wild-type and FOLFOXIRI.[34, 43-46] With respect to current data oxaliplatin-based chemotherapy combined with cetuximab and oral or bolus FP (e.g. XELOX or Nordic-FLOX) should be avoided.[34, 47] Despite the increase of 10% in response rate, if bevacizumab is added to IFL, triplet combination with oxaliplatin-based regimen does not seem to be recommendable in patients requiring tumour shrinkage.[48, 49] However, definite information about comparative efficacy of bevacizumab or anti-EGFR antibody combination with chemotherapy (FOLFOX/FOLFIRI) will be soon available from the US Intergroup trial (CALGB/SWOG 80405).

With the clinical development of new drugs e.g. aflibercept (VEGF-trap), with proven activity in second line, if added to FOLFIRI, even after bevacizumab failure,[50] further treatment options might be available in the future. Furthermore, four drug combinations with FP, irinotecan and oxaliplatin combined with either cetuximab/panitumumab or bevacizumab are currently investigated, with high response and disease control rates in single arm Phase II trials.[51-54]

Patients with symptomatic, aggressive disease (group C) should receive an active two- to three-drug regimen as first-line treatment.

For asymptomatic and never resectable, or co-morbid patients (group D) single-agent FP with or without bevacizumab or single-agent anti-EGFR antibody (or even watchful waiting) represents a reasonable alternative to an intensive first line treatment.[55-58] Current sequential approaches with fluoropyrimidines, oxaliplatin, and irinotecan, comparing single agents with upfront combinations (CAIRO, FOCUS, LIFE) show improved response and PFS with upfront combination treatment, and similar OS for both approaches, and may therefore be an option for patients not requiring tumour shrinkage.[59-61] Comparable results could be shown in an elderly and frail population in the FOCUS 2 trial.[62]

Synchronous Metastatic Disease

Management of synchronous disease is changing in terms of leaving an asymptomatic primary tumour *in situ* and starting with upfront systemic treatment pursuing a curative approach for either initially or potentially resectable disease (liver and/or lung metastases) and avoiding mutilating surgery in unresectable disease.[41, 63, 64]

Treatment Duration/Maintenance/Intermittent Treatment

Treatment should be continued according to the individual situation, patient's needs, cumulative toxicity (in particular neurotoxicity with oxaliplatin), and aggressiveness of the disease. Survival is not relevantly impaired if first-line combination treatment with all drugs is not given continuously until progression. If secondary resection is either not possible owing to patient factors or not feasible owing to disease characteristics, continuation of combination chemotherapy (in particular oxaliplatin) beyond three to four months is not recommended. Pre-planned treatment intervals and break duration ("intermittent treatment") or discontinuation after three months and restart of treatment in case of progression ("stop and go") are possible options.[65-68] Treatment might either be completely discontinued, or the less toxic drug (e.g. single agent FP and/or bevacizumab) might be continued as maintenance. Patients with liver limited disease as well as aggressive disease, with poor prognostic features e.g. elevated platelet count (>400.000 per µl) or LDH, more

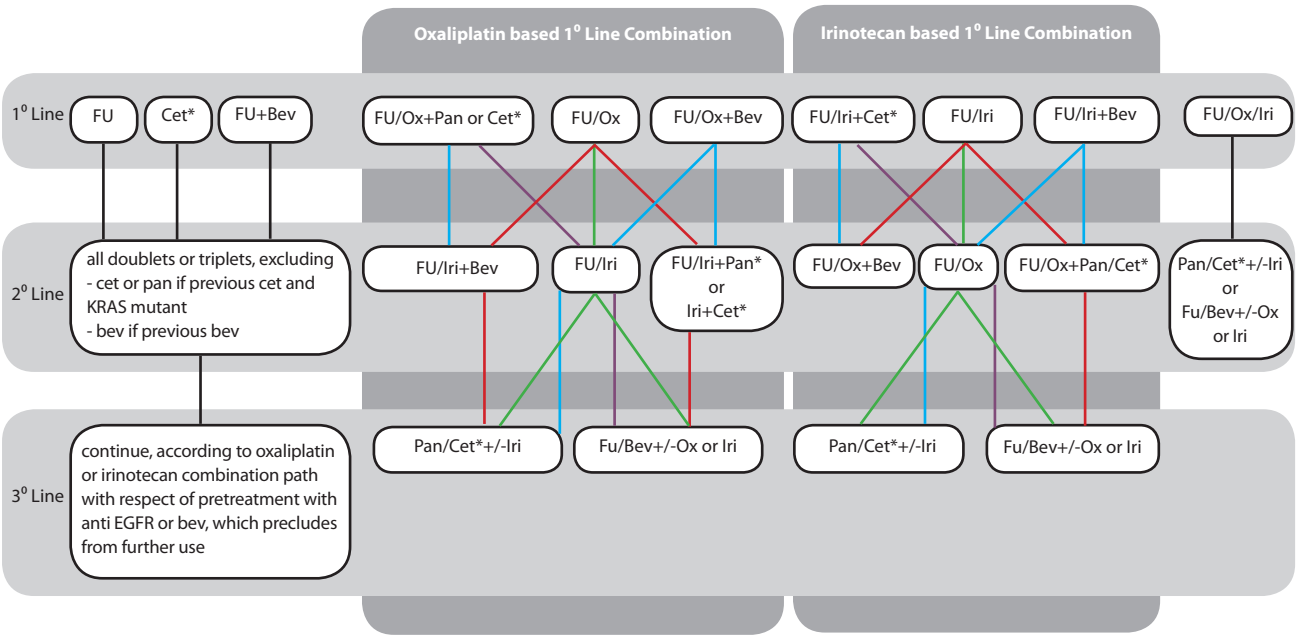

Figure 1. Course of treatment beyond first line. (*only KRAS wt; FU: fluoropyridmidines, Iri: irinotecan, Ox: oxaliplatin, Bev: bevacizumab, Cet: cetuximab, Pan: panitumumab) (adapted from ESMO CRC consensus 2011, *Annals of Oncology* in press)

than two metastatic sites after three months of oxaliplatin containing induction, seem to have a substantial loss if treatment is completely discontinued, therefore these patients should receive maintenance treatment.[67-69] Results of the ongoing CAIRO3 and AIO 0207 studies may help in defining the use of maintenance vs. observation after 4.5–6 months of induction chemotherapy.

Second and Further Line Treatment

The algorithm for choice of second line treatment is mainly based on the applied first line regimen (see Figure 1), and again treatment aim and clinical patient factors (co-morbidity, toxicity, etc). Despite the currently available drugs, further agents might prove successful salvage treatments in the future, e.g. regorafenib.

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Minimally Invasive Surgery of Liver Neoplasms

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Introduction

Laparoscopic liver resection was first reported in the early 1990s.[1, 2] Perfection in laparoscopic techniques and technological advances in laparoscopic equipment have significantly extended the surgeon's ability to perform the procedure safely. This together with accumulated experiences and encouraging literature reports has broadened indications to laparoscopic techniques. However, laparoscopic liver resection is still fully presented only in a few expert centres around the world.

Indications

Current indications to laparoscopic liver resections have nearly reached classic indications to open liver resection.[3, 4] They include benign and malignant liver lesions, and living donor liver harvesting. Very large tumours or the need for vascular reconstruction have been regarded as the only contraindications to laparoscopic liver resection. A lack of expert surgeons in the field of laparoscopic liver surgery and insufficient hospital capacities have made a considerable influence on the actual spread of laparoscopic approach.

Technical Considerations

The majority of centres apply mainly total laparoscopic liver resections, whereas hand-assisted resections and laparoscopic-assisted open liver resection (hybrid resection) are used in routine practice in other centres.[5-7] So far there is still no agreement about indications to hand-assisted or hybrid liver resection. The hand assistance enabling tactile sensation may be applied to avoid conversion in technically challenging cases. However, these techniques diminish the minimally invasive nature of the procedure, beside high expertise in intraoperative ultrasonography could largely substitute the lacking tactile sensation during totally laparoscopic resection.[8, 9]

Recent studies have shown similar perioperative and long-term outcomes of anatomic and non-anatomic-liver resection concerning both colorectal liver metastases and hepatocellular carcinoma. The margin width is important in the resection of hepatocellular carcinoma, while in resection of colorectal liver metastases clear surgical margin is sufficient for the treatment.[10]

Wide liver resection involves a substantial reduction of hepatic parenchyma that can lead to clinical manifestation of decompensation, including liver insufficiency.[11] The extent of liver resection correlates with the rate of postoperative complications[12] and it is associated with higher tumour recurrence rate due to amplified activation of regenerative growth factors.[13]

Haemihepatectomies are associated with significantly increased technical demands. In spite of the intraoperative technical challenges of major resections, the laparoscopic approach provides improved postoperative course to the patients. A recent multicentre study including 210 patients has reported promising clinical outcomes of laparoscopic haemihepatectomies with mortality below 1% which corresponds to the best outcomes reported in open surgery.[14]

The resections of so called posterosuperior segments (I, VII, VIII,

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IVa) are considered to be technically difficult because of poor exposure. Many centres still do not consider these lesions for laparoscopic approach, others are inclined to have a recourse of the hand-assistance in such cases. However, it has been shown that by application of appropriate adjustment of surgical techniques, patient positioning and special equipment, it is possible to reach outcomes similar to procedures in easy accessible segments.[8, 15]

Intraoperative Issues

Operative time varies significantly between the studies reflecting to both types of performed resections and accumulated experience/technical skills. Operative time is usually within 100-250 minutes in general and it corresponds to time reported for open reciprocal liver resection.[16, 17]

Difficulties in achieving haemostasis during liver parenchymal transection have been a major challenge for surgeons. The blood loss varies fairly from centre to centre and comprises around 200-400 ml. It trends to be lower at laparoscopic approach than at open resection resulting in decreased requirements for blood transfusion.[16, 17] Though intraoperative bleedings occur rarely, they could be more difficult to manage due to the lack of manual compression, occasionally necessitating conversion to open procedure. Major blood loss, and the need for blood transfusion in particular, increases a risk of postoperative morbidity and mortality.[18, 19] The control of resection by laparoscopic ultrasonography plays a crucial role to avoid accidental vascular and biliary injuries and to secure resection margins.[9]

Theoretical premises and experimental studies have led to concerns among clinicians concerning a potential risk of gas embolism during laparoscopic liver resection which was especially underlined in regard to posterosuperior segments.[20] This risk has been greatly overestimated.[21] However, there is still lack of sufficient knowledge in this area.

The conversion rate reported in the literature is in a range of 2-15%.[16, 17] However, with surgical experience the conversion rate reduces and currently does not exceed 5% in expert centres. The main reason for conversion was bleeding, fatal haemorrhage has been reported to be the most serious intraoperative incident.

While postoperative complications are well reported in the literature, small emphasis has been made to registration and reporting intraoperative incidents/complications which do not require conversion. Bowel perforation is an intraoperative incident which can be managed without conversion in the majority of cases.[7]

The Pringle manoeuvre and other methods of intraprocedural vascular occlusion with intent to decrease blood loss are widely used for laparoscopic liver resection, such as for open resection.[22] However, the contemporary transection equipment and advanced operative techniques have made routine use of vascular occlusion redundant.[7, 23]

Postoperative Course

Laparoscopic liver resection is associated with considerable reduction in postoperative pain and hospital stay, faster diet resumption, time to ambulation after surgery and beneficial cosmetic outcomes.[16, 17] Postoperative hospital stay comprises of five to eight days in average depending largely on non-medical issues (health system, institutional routines). It has been shown that median postoperative hospital stay could be only three days.[7, 24] Combination with the fast track surgery could further shorten hospital stay down to one to two days.[25]

Perioperative mortality of laparoscopic liver resection is below 1% corresponding to the best outcomes reported for open surgery.[16] Postoperative complication rate comprises around 10-15% and is reported to be similar or less frequent than observed in open liver resection.[16, 17] Postoperative bile leak develops in about 1.5% and represents typical crucial complication for laparoscopic liver resection as well as it does for open surgery. Bile leak is usually managed by percutaneous drainage and bile duct stenting. Postoperative intra-abdominal bleeding is a very rare but threatening complication, that can mainly be managed via re-laparoscopy. Although liver resection specific complications were reported in a similar rate with open surgery, the rate of liver decompensation among cirrhotic patients has a trend to decrease at application of laparoscopic approach.[26, 27] General morbidity - cardiopulmonary complications, abscesses and wound complications have a tendency to decrease in application of laparoscopic approach.[26, 28-30] Rate of incisional hernias after laparoscopic liver resection is appreciably lower then after the open counterpart.[22, 31]

Laparoscopic Liver Resection in Transplantation Surgery

In patients with hepatocellular carcinoma, previous liver resection may compromise subsequent liver transplantation by creating adhesions and increasing surgical difficulty. Initial laparoscopic resection may reduce such technical consequences. It was shown that application of laparoscopic techniques facilitates subsequent liver transplantation and was associated with reduced operative time, blood loss and transfusion requirements compared with transplantation subsequent to open initial resection.[32]

Laparoscopic techniques showed its role in harvesting of living donor liver for transplantation.[33, 34] Early comparative studies have verified similar safety of such approaches compared with conventional open harvesting.[34] The laparoscopic procedure was associated with significantly decreased blood loss but increased operative time. However with surgical experience the operative time is likely to considerably reduce.

Oncologic Outcomes

Whereas there is no doubt to prefer the laparoscopic approach over open counterpart for benign liver lesion, some concerns may arise in

regard to malignant liver lesions.[35] One can expect improved oncologic outcomes after application of laparoscopic techniques due to less invasive intervention and therefore less stress response, less immunologic alterations and minor activation of regenerative growth which promotes tumour recurrence.[36, 37] However these theoretical and experimental premises have to be confirmed in clinical settings. One disadvantage of laparoscopic resection is the possibility to miss additional liver lesions however application of modern dynamic CT and MRI scans as well as proper intraoperative ultrasonography the risk should be minimal.[16]

Concerns about the adequacy of surgical margins and possible tumour seeding prevented the widespread adoption of laparoscopic techniques for liver malignancies in earlier years. Comparative studies concluded that, there was no difference in resection margin magnitude and rate of margin-free resections between laparoscopic and open liver resection.[22, 28, 38-41] Besides, the extent of surgical margin has been questioned and at present the tumour free margin or R0 resection should be adequate for colorectal metastases.[42] This reinforces the idea about parenchyma-sparing technique and its posibility to do increased amount of repeated resections when new metastasis occurs.[43] In hepatocellular cancer the development of micrometastases depends on tumour size and histological grade necessitating a margin width of at least 1 cm and above.[44] Apropos, no incidence of port-site recurrence or tumour seeding has been reported.[45, 46] Intraoperative laparoscopic ultrasound control of tumour location and resection line are considered crucial in this context.[9, 47]

Liver resection is generally accepted as the standard of care and may cure patients with colorectal metastases.[48, 49] For patients with hepatocellular carcinoma, who do not meet transplantation criteria, liver resection offers the next best survival rate.[50, 51] Many centres have reported surgical and middle-term oncologic outcome of laparoscopic resection of colorectal liver metastases and hepatocellular carcinoma. Only a few centres have reported long-term outcomes including five-year overall, recurrence-free and disease-free survivals along with recurrence pattern (Figure 1). Three-year and five-year overall survival for both pathologies are reported around 70-80% and 50-60% respectively.[43, 52-58]

Recurrence pattern has shown to be similar to the pattern described for open resection of colorectal liver metastases and hepatocellular carcinoma, whereas long-term outcomes are at least as good as reported for open liver resection.[53, 55, 56, 59, 43]

As mentioned earlier, laparoscopic technique has contributed in a higher rate of repeat liver resections after recurrences, in addition treatment of both recurrences of the primary tumour and recurrences in other organs has become more aggressive.[43, 48, 60-62] The combination of laparoscopic resection and parenchyma-sparing technique will probably lead to an additional increase in the rate of repeated resections in the treatment of colorectal metastasis. Thus many recurrences are treated nowadays.[43, 63] Important to note in this regard is that classical definition of cancer-related survival after surgery does not distinguish between recurrence-free survival and disease-free survival (disease-free survival typically corresponds to recurrence-free survival in our definition). This concept of distinguishing between recurrence-free and disease-free survival is not new, and it was earlier accidentally applied in surgical oncology.[63] However, multiple and repeated interventions and parenchyma-sparing techniques in patients with primary and especially with metastatic cancer in the liver have been discussed and performed over the last decade. It is therefore necessary to distinguish between the terms "recurrence-free" and "disease-free survival" in order to justify the new approach and to get more precise documentation of oncologic outcomes.

A recent tri-institutional study showed similar surgical outcomes after repeat laparoscopic liver resection compared with outcomes reported for primary resections.[62] This study verified that the sub-group of patients having laparoscopic primary liver resection was associated with decreased median blood loss (290 vs. 400 ml) and lower rate of blood transfusions. Tumour involved resection margins were reported in 9% and five-year survival in sub-group of patients with colorectal metastases was 55%.

There have not been any prospective randomised controlled trials published which compare the oncologic outcome of laparoscopic liver resection to open resection. The present knowledge is mainly based on

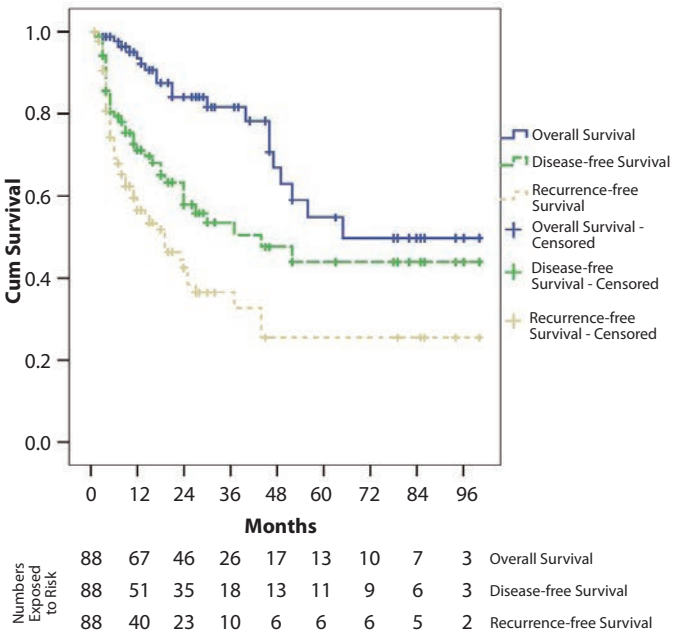

Figure 1. Kaplan-Meier survival curves of patients with laparoscopically resected colorectal liver metastases, outcomes the world's major published single centre series (from Kazaryan AM, Marangos IP, Røsok BI, *et al*. Laparoscopic resection of colorectal liver metastases: surgical and long term oncologic outcome. Ann Surg 2010;252:1005–1012; reproduced with permission).

First Authors, Year	Country	Journal	Number of Patients	3-year Overall Survival, %	5-year Overall Survival, %
Colorectal Metastases					
Nguyen, 2009	Multi-centre study: USA, France	Ann Surg	109	69	50
Kazaryan, 2010	Single-centre study: Norway	Ann Surg	107	68	51
Casting, 2009	Two-centre study: France	Ann Surg	60	82	64
Shafaee, 2011	Tri-centre study: France, Norway, USA	J Am Coll Surg	55*	83	55
Vibert, 2006	Single-centre study: France	Br J Surg	41	87	-
Sasaki, 2009	Single-centre study: Japan	Br J Surg	39	64	64
Hepatocellular Carcinoma					
Dagher, 2010	Tri-centre study: France, Italy	J Am Coll Surg	163	93	65
Chen, 2008	Two centre study: Taiwan	Ann Surg Oncol	116	74	62
Yoon, 2010	Single-centre study: Korea	Surg Endosc	69	91	
Belli, 2011	Single-centre study: Italy	Dig. Surg.	65	68	39
Bryant, 2009	Single-centre study: France	Ann Surg	63	70	60
Tranchart, 2010	Single-centre study: France	Surg Endosc	42	74	60
Sasaki, 2009	Single-centre study: Japan	Br J Surg	37	73	53
Truant, 2011	Single-centre study: France	Surg Endosc	36		34

Table 1. Middle- and long-term survival after laparoscopic liver resection for malignant lesions (studies with over 35 cases).
* repeat resections

short-term, non-randomised comparative studies or historical comparison with outcomes of open surgery. An alternative way is to score patients by the current most reliable systems of survival prognosis and use a calculated survival as a reference to compare with achieved survival after laparoscopic liver resection. Implementation of such an approach showed improved oncologic outcomes after laparoscopic liver resection for colorectal liver metastases.[43]

One could probably transfer oncologic integrity of laparoscopic liver resection, revealed for colorectal liver metastases and hepatocellular carcinoma, to other malignancies such as cholangiocarcinoma and metastatis to the liver from other malignancies. Such cases were reported in small series,[7, 26, 58, 64, 65] three-year survival was reported to comprise 50% after laparoscopic resection of liver metastases from neuroendocrine gastrointestinal tumours.[65] This corresponds to survival reports reported for open liver resection in patients with neuroendocrine liver metastases.[66, 67] Survival data from the major studies are summarised in Table 1.

Conclusions

Tremendous advances have taken place in the field of laparoscopic liver surgery. It is now apparent that laparoscopic techniques in liver resection is as safe as open techniques. The benefits of the laparoscopic approach include less analgesic requirements, shorter hospital stay, decreased transfusion requirements, faster recovery, better cosmetic outcome and less adhesions which subsequently facilitates repeat resections. The oncological results of laparoscopic surgery seem to be similar or possibly better to those after an open approach.

Indications for laparoscopic liver resection are nearly the same as for open surgery, and technical feasibility has been reported as the most important limiting factor. There are few expert centres worldwide, but the propagation of the technique is growing.

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Renal Denervation for Resistant Hypertension

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Introduction

Despite progress in recent years in the prevention, detection, and treatment of high blood pressure (BP), hypertension remains an important public health challenge.[1] Hypertension affects approximately one billion individuals worldwide. With the exception of relatively rare monogenetic forms, there is general agreement that the condition is multifactorial. High BP is associated with an increased risk of mortality and morbidity from stroke, coronary heart disease, congestive heart failure, and end-stage renal disease; it also has a negative impact on the quality of life. Hypertension cannot be eliminated because there are no methods to prevent the development of hypertension, but its incidence can be decreased by reducing the risk factors for its development, which include obesity, high dietary intake of fat and sodium and low intake of potassium, physical inactivity, smoking, and excessive alcohol intake. For established hypertension, efforts are to be directed to control BP by lifestyle modification. However, if BP cannot be adequately controlled by these activities, a pharmacotherapy can be instituted. Normalisation of BP reduces cardiovascular risk (for cardiovascular death, myocardial infarction, and cardiac arrest), provides renoprotection (prevention of the onset or slowing of proteinuria and progression of renal dysfunction to end-stage renal disease in patients with hypertension, diabetes mellitus types 1 and 2, and chronic renal disease), and decreases the risk of cerebrovascular events (stroke and cognition impairment), as has been widely demonstrated by a large number of randomised clinical trials.[2] Thus, a BP reduction of 5 mmHg reduces the risk of stroke of about 34%. But, if this approach works for many, it fails in a considerable number of patients for various reasons, including drug-intolerance, noncompliance, physician inertia, and others, leaving them at unacceptably high cardiovascular risk.

Resistant hypertension is defined as blood pressure that remains above goal inspite of combined use of three antihypertensive agents of different classes. Thus, patients whose blood pressure is controlled with four or more medications should be considered to have resistant hypertension. If tolerated, one of the three agents should be a diuretic and all agents should be prescribed at optimal doses. Goal blood pressure is less than 140/90 mmHg in average risk hypertensive patients

As much as one third of patients with arterial hypertension are treatment refractory as they do not reach a sufficient blood pressure control despite antihypertensive combination therapy.[3, 4] There are many classes of antihypertensive drugs and new compounds in the established drug classes are likely to widen the armamentarium available to combat hypertension. These include the aldosterone receptor-blockers, diuretics, vasodilator, beta-blockers, renin inhibitors, endothelin receptor antagonists, and dual endopeptidase inhibitors. The use of fixed-dose combination drug therapy is likely to increase but sometimes it is not enough to control BP. Understanding the patogenic mechanisms responsible for hypertension in these conditions may lead to improved and more targeted therapeutic interventions. Several factors have been implicated in the pathogenesis of hypertension.[5, 6] Although the role of sodium retention, total body volume expansion, and hyperactivity of the renin-angiotensin-aldosterone system (RAAS) are well recognised, increasing evidence suggests that afferent impulses from the kidney may increase sympathetic nervous system activity in areas of the brain involved in noradrenergic regulation of blood pressure and contribute to the development and maintenance of hypertension.[7] The renin-angiotensin-aldosterone system plays a key role in BP elevation in the early phase of hypertension, either in the presence of kidney disease or in normal kidneys.[8] Later on, other mechanisms such as sodium retention and activation of the sympathetic nervous system (SNS) may contribute to hypertension and they have long been recognised as the most important factors.[9-11] The kidney is richly innervated with baroreceptors and chemoreceptors. Renal afferent nerves are connected directly or indirectly to a number of areas in the central nervous system that contribute to BP regulation (Figure1).[12, 17] Stimulation of renal receptors by adenosine, urea, or electrical impulses evoke reflex increases in SNS activity and BP.[13, 14] Mechanisms responsible for increased SNS activity include intrarenal stimulation of renal afferent nerves, direct central effects of angiotensin II, oxidative stress, cytokines, and NO inhibition. Also kidney damage can raise BP even in the absence of renal insufficiency; there is what happens in the pathogenesis of hypertension observed in patients with chronic kidney disease (CKD) caused, for example, by polycystic kidney disease.[15]

Identification of the factors responsible for the intrarenal activation of these afferent pathways, or for the stimulation of sympathetic output from the brain, may lead to a new understanding of the pathophysiology of sympathetic overactivity and hypertension and, hopefully, to novel therapies based on specific inhibitors of these activating factors. The abolition of renal nerve activity could attenuate the prolonged enhancement of renin secretion and renin gene expression. Renal nerve activity thus appears to contribute importantly to background stimulation of renin secretion and renin synthesis. This stimulation is normally masked by the inhibitory effect of ambient blood pressure. Recently, renal sympathetic denervation (RSD) using a percutaneous, catheter-based radiofrequency ablation, was shown to be beneficial in patients with resistant hypertension.[16-19] Data from various studies have shown that sympathectomy has efficiently lowered blood pressure and prolonged the life expectancy of patients with hypertension.[16, 17, 20]

This article will review the recent literature regarding catheter-based renal ablation in the context of current knowledge of the pathophysiology of resistant hypertension, and will explore future directions for research regarding this new approach.

Renal Sympathetic Denervation

The renal sympathetic denervation (RSD), an interventional minimally invasive procedure, via femoral artery access, has became available to precisely ablate afferent and efferent sympathetic nervous fibres surrounding the renal artery. The procedure is feasible and safe. Via an ablation catheter with an electrode tip and a radiofrequency generator (Symplicity by Ardian Inc., Palo Alto, CA, USA), a series of four to six ablation sites are administrated in both renal arteries leading to denervation of the sympathetic nerve fibres while keeping the renal artery intact.[21] Preclinical studies performed by Ardian Inc. in young swine reported the effectiveness of this technique at achieving renal denervation without causing significant vascular or renal injury up to six months following the procedure.[17] Surgical sympathectomy, performed in the early 1950s, did have high morbidity and mortality, as well as bowel, bladder, and erectile dysfunction and postural hypotension. Renal denervation with radiofrequency (RF) could be a viable therapeutic option not only for patients with resistant hypertension, but also for patients with other diseases thought to be associated with hyperactive renal sympathetic and afferent activity, such as chronic kidney disease and congestive heart failure. These advantages include short procedural and recovery times, the use of a minimally invasive approach and the localisation of the procedure to the kidney, thereby avoiding the systemic side-effects that have plagued patients in the past.[18]

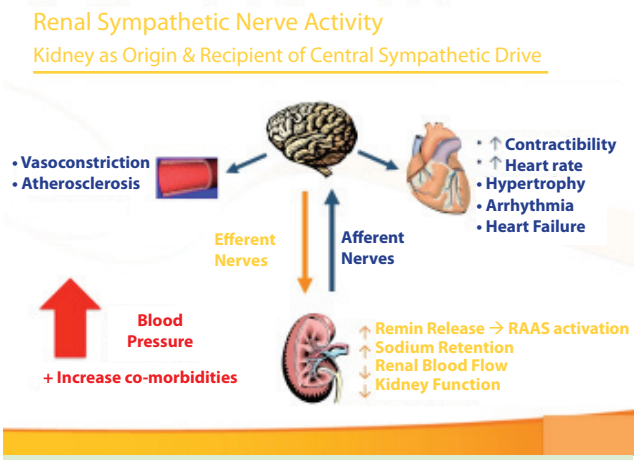

Figure 1. Renal afferent nerves are connected directly or indirectly to a number of areas in the central nervous system that contribute to BP regulation.

The randomised controlled Symplicity-HTN-2 trial[20] provides important information to determine the role of this new method for the treatment of drug resistant hypertension. An initial cohort study, performed by Krum *et al*.,[17] demonstrated the efficacy of this novel catheter-based device at producing both renal denervation and corresponding, clinically and statistically significant reductions in blood pressure over a 12-month period (reductions of 14/10, 21/10, 22/11, 24/11, and 27/17 mmHg at one, three, six, nine, and 12 months, respectively), without serious adverse effects, in a group of 45 patients who met specific clinical criteria for resistant hypertension (blood pressures of ≥160 mm Hg, or ≥150 mm Hg for patients with type 2 diabetes, despite compliance with three or more antihypertensive drugs, including a diuretic). Periprocedural complications were rare and all of them were related to the percutaneous technique, rather than the radiofrequency ablation. Following this work, the Symplicity HTN-2 investigators (Esler *et al.*[16]) performed a more recent randomised controlled trial, the Symplicity HTN-2 Trial, to study the effectiveness and safety of catheter-based renal denervation with the Symplicity Catheter System to reduce blood pressure in a similar, but larger, population of patients with resistant hypertension, defined using the same criteria as the previous study by Krum *et al*.[17] This study of 106 patients, each randomly allocated either to undergo renal denervation with previous treatment, or to maintain previous treatment alone (control group), found a 33/11 mmHg reduction in blood pressure in the renal denervation group compared to the control group at six month follow-up ($p < 0.0001$ for systolic and diastolic blood pressure). Results of this important study further support those from Krum's study regarding the effectiveness of catheter-based renal denervation at reducing blood pressure in patients with resistant hypertension. As in the previous one, in this study there were limited acute and chronic procedural complications, there was no statistically significant difference in the change in renal function at six months between the two groups and there were any occurrence of new stenosis (>60% occlusion confirmed by angiogram) at the sites of radiofrequency delivery. They reported only five "serious adverse events" requiring hospital admission in patients who underwent renal denervation (compared to three controls with such events); these included both hypotensive and hypertensive episodes, as well as a transient ischaemic attack, angina requiring a coronary stent, and one episode of nausea and oedema perhaps relating to underlying hypertension,

but these adverse events are maybe acceptable in the context of the expected benefit of the procedure for the individual patient.

In our experience, we had, in all cases performed, procedural success without major complications. We reported 10 mmHg decrease in BP already at two months follow-up but we need more cases and a longer follow-up.

Technique

The Ardian Symplicity® Catheter is composed by: 1) disposable catheter to deliver RF energy to the target site; 2) generator (G2 model) which automatically checks the RF delivering; 3) foot pedal to activate the system, without the use of hands.

Symplicity ® Disposable Catheter

The disposable catheter is designed to deliver low-power radiofrequency energy which allows the denervation of the renal artery wall. The catheter can be placed in the renal artery (Figure 2) through a 6-French guide catheter; it is flexible and has an adjustable tip that could be curved and turned, to allow the best contact with the vessel wall. It does not require additional cable to connect it to the generator.

Before performing the denervation, you should confirm the absence of renal artery stenosis and consider the minimum diameter of the artery (four mm) to make the process safe. There are generally four to six ablations per artery and they are carried out starting at about five mm from the bifurcation and remaining at about five cm from renal artery origin. Each ablation takes about two minutes, and usually results in a kind of visceral abdominal pain that is relieved by analgesics. The RF is applied in various points on the vessel wall, following a spiral movement, so you can interrupt a greater amount of fibres. Exact intervals of impedance, temperature, time and energy supply should be maintained, but the system is very reliable because it has a security algorithm that, if necessary, can cut-off the energy supply.

Symplicity ® Generator

The generator is an electrosurgical device with a high degree of automation for ablation of renal sympathetic nerves interventions. It operates through RF energy and, in accordance to a programmed algorithm, it automatically stops the emission of RF energy at the end of treatment. During RF delivery, power is monitored and controlled continuously depending on the temperature and the impedance measured on the specific site of ablation.

Foot Pedal

The foot pedal allows the activation of the generator without the use of hands.

Discussion

Preliminary clinical results suggest that catheter-based renal denervation utilising the Symplicity catheter could be a feasible,

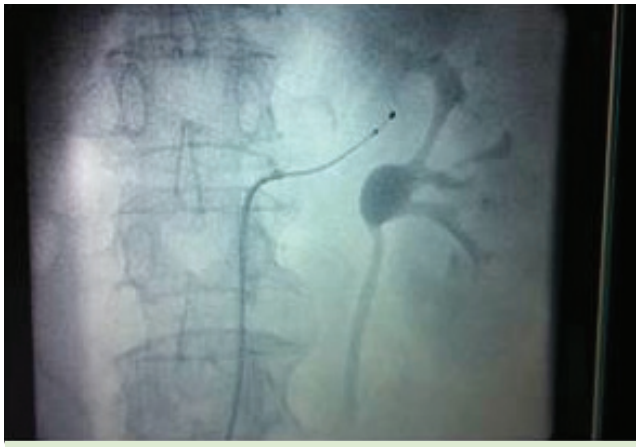

Figure 2. The figure shows the ablation catheter in the left renal artery.

effective and safe therapeutic option for patients with resistant hypertension.[16, 17, 22, 23] In the Symplicity HTN-2 Trial, 84% of patients achieved a 10 mmHg decrease in systolic blood pressure (compared with 35% of controls) and 39% achieved a systolic blood pressure of less than 140 mmHg at six months (compared with 6% of controls) (Figure 3).[16] Additionally, a small percentage of patients experienced adverse events and the estimated glomerular filtration rate remained stable. The decrease in arterial pressure after renal denervation is associated with decreased peripheral sympathetic nervous system activity, suggesting that the kidney is a source of significant central sympathetic outflow via afferent renal nerve activity. The renal sympathetic denervation, aiming to modulate renal sympathetic nerve activity, produces a substantial and sustained reduction in blood pressure. However, there are many questions that must be answered regarding the technique's effectiveness and safety before the stable acceptance of this approach in the clinical setting. For-example, the follow-up is essential in measuring the long-term impact of this technique and a longer follow-up is required to measure cardiovascular impact. Despite this catheter-based renal sympathetic denervation shows great promise as a safe and effective therapeutic technique for patients with resistant to therapy hypertension.

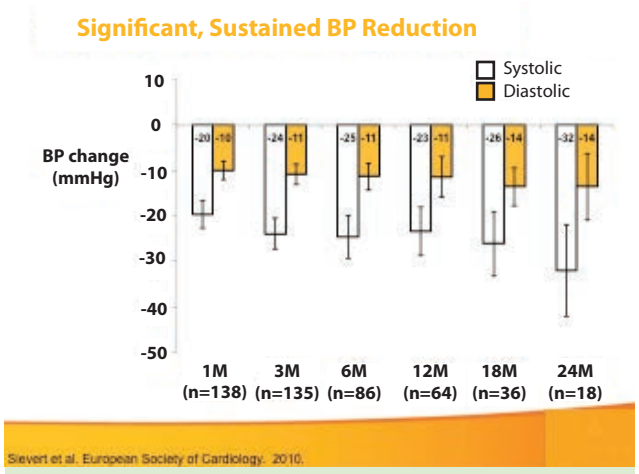

Figure 3. Symplicity HTN-2 Trial:results.

Conclusions

Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients. It should be accompanied by a decreased requirement of antihypertensive medications and a reduction of all the organ complications produced by a long-standing hypertension.

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Early Detection of Upper Gastrointestinal Tumours Based on Molecular Analysis of p53 Expression

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Oesophageal carcinoma is one of the most lethal malignancies known. In the last year, the incidence of adenocarcinoma of the oesophagus, like adenocarcinoma of the gastric cardia, is increasing rapidly. The prognosis of oesophageal and gastric cancer patients depends mainly on three variables: depth of invasion, lymph node metastases and distant metastases. Tumoural infiltration of the wall and involvement of lymph nodes are closely interconnected. Long-term survival after surgical treatment for carcinoma of the upper digestive tract is related to the pathological stage of the tumour. The rate of endoscopic detection of superficial gastrointestinal carcinoma is still unsuccessful. At present, it is clear that mass screening can not be used for upper gastrointestinal cancer. It is now generally accepted that upper gastrointestinal tumours develop from a premalignant lesion. However we must aim at the selection of high-risk patients.

p53 plays a crucial role in cellular proliferation and apoptosis and as the guardian of genomic integrity. Molecular analysis of p53 might help to identify patients from high risk population at an early stage of malignant transformation.

Patients and Methods

In this prospective study we analysed histologic paraffin embedded tumour material obtained from 28 patients with upper digestive tract cancer (study group); 5 with oesophageal squamous cell carcinoma, 23 with adenocarcinoma of gastro oesophageal junction and 13 patients with non-cancer lesion or normal tissue of upper digestive tract tissue (control group). Informed consent was obtained from each of the patients prior to his/her participation in the study (from February 2004 to November 2005).

The inclusion criteria for the study were histologically confirmed oesophageal or/and gastric cardia cancer. The exclusion criteria were metastatic disease, preoperative chemo and/or radiotherapy.

Histopathologic Examination

The pathologic TNM staging (pTNM) were determined by an experienced pathologist according to the International Union Against Cancer (UICC) 2002 criteria. Tumour type and differentiation were classified according to World Health Organization criteria. Grade of differentiation of the carcinoma was also analysed, and well- (G1), moderately- (G2), and poorly-differentiated (G3) tumours were distinguished. Microscopic examination was based upon routine haematoxylin and eosin (H&E) staining.

For the purpose of the present study, gastric cardia tumours were retrospectively classified according to the Siewert classification based upon both the macroscopic appearance during the surgical procedure and the detailed pathological record.

Immunohistochemical Staining

Immunohistochemical staining was performed on routinely processed paraffin primary tumour sections using the following primary antibodies: monoclonal p53 protein clone DO-7 (Dako Cytomation). P53 was evaluated by two categories: intensity (grade of staining- 0, 1, 2, 3) and diffusion (part of cell involved in reaction- 0, 1 less 30% of cell, 2-30-70%; 3– more than 70% of cell) (Figures 1 and 2).

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Statistical Evaluation

Statistical analysis were performed using Cox proportional hazards model. The association between the antigen expression and pathological features was evaluated by the Mann–Whitney U test for two independent samples. Survival rates were calculated according to the Kaplan–Meier method and are presented herein as observed overall survival, including post-operative deaths. Significant differences in survival were determined using the log rank test. All statistical analyses were performed on a personal computer using Statistica for Windows 5.0 (StatSoft, USA, 1999).

Results

Detailed patient characteristics are summarised in Table 1. The available data do not suggest the existence of a familial history of cancer in these patients. Complete surgical resection was performed for all patients. No statistically significant correlation was found between the expression of a P53 and the parameters of the primary tumour – grade of differentiation or its spread as reflected in the TNM classification (p=0,08341, p=0.341).

But p53 expression was significantly higher in the cancer tissue than in normal (p=0,005206 for diffusion, p=0,019392 for intensity). For defining potential distinctions we marked out a sub-group gastric cardia cancer and compared it with the control group (Table 2a).

As a next step we compared the p53 expression between oesophageal and gastric cardia group (Table 2b).

No significant difference was observed in p53 expression between oesophageal and gastric cardia cancer (both for diffusion and intensity) (Table 3). We compared also p53 expression between different types of gastric cardia cancer (Table 4).

Additionally we made analysis of p53 expression with relation to its prognostic importance. We found no association between p53 expression and median survival of oesophageal and gastric cardia patients (P53 intensity p=0,354701191186905, P53 diffusion p=0,630432) (Table 7).

Median survival was higher in cardial than oesophageal cancer (p=0,004): Siewert-II – 20 months, Siewert-I – 18 month, Siewert-III – 15 month, oesophageal cancer – 3,3 month (Figure 3).

Conclusions

In upper digestive tract tumours the certain peculiarities in p53 expression exist. There is no statistical validity of p53 expression distinction depending on tumour site. P53 expression does not indicate prognosis of patients with upper digestive tract tumours.

P53 examination in biopsy specimens taken during endoscopies in

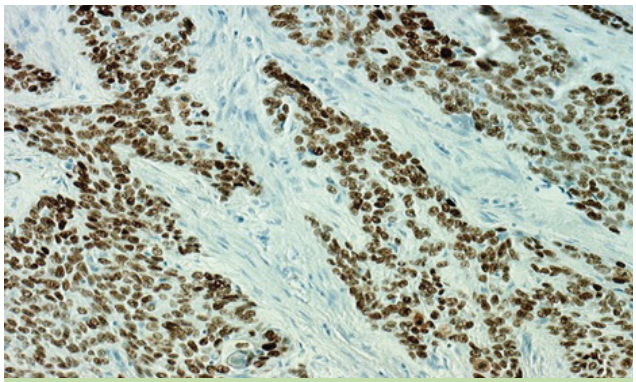

Figure 1. Pathologic immunohistochemistry p53 labelling result of Oesophageal squamous cell carcinoma: intensity 3, diffusion 3 (×1000 magnification).

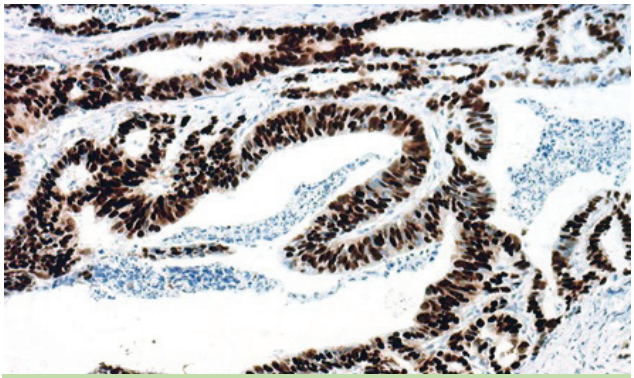

Figure 2. Pathologic immunohistochemistry p53 labelling result of gastric cardia adenocarcinoma: intensity 3, diffusion 3 (×1000 magnification).

Characteristics	No
Age (median years)	59
Gender	
Male	26
Female	2
Tumour Stage	
1-2	11
3-4	17
Grading	
Well	8
Moderate	9
Poor	11
Tumour Site	
Upper oesophagus	5
Oesophagogastric junction cancer (total)	23
Siewert-I	7
Siewert-II	8
Siewert-III	8
Histology	
Squamous Cell	8
Adenocarcinoma	20

Table 1. Characteristics of patients with upper digestive tract cancer.

		Pattern of P53 espression				
		0	1	2	3	P value
P53 intensity	Study Groups (pts)	9	4	1	14	0.005206
	Control Groups (pts)	9	4	0	0	
P53 diffusion	Study Groups (pts)	9	6	5	8	0.019392
	Control Groups (pts)	9	2	2	0	

Table 2a. Comparing expression p53 in study group and control group.

		Pattern of P53 espression				
		0	1	2	3	P value
P53 intensity	Study Groups (pts)	8	3	1	11	0.012
	Control Groups (pts)	9	4	0	0	
P53 diffusion	Study Groups (pts)	8	5	5	5	0.04343
	Control Groups (pts)	9	2	2	0	

Table 2b. p53 expression comparing gasric cardia cancer with control group.

		Pattern of P53 espression				
		0	1	2	3	P value
P53 intensity	Oesophageal Cancer (pts)	1	1	0	3	0.800618
	Gastric Cardia Cancer (pts)	6	2	0	10	
P53 diffusion	Oesophageal Cancer (pts)	1	1	0	3	0.363
	Gastric Cardia Cancer (pts)	6	4	3	5	

Table 3. Oesophageal and gastric cardia comparison.

		Pattern of P53 espression				
		0	1	2	3	P value
P53 intensity	Siewert-1 (pts)	2	1	1	3	0.69432789
	Siewert-2 (pts)	2	1	0	5	
P53 diffusion	Siewert-1(pts)	2	1	2	2	0.95508933
	Siewert-2 (pts)	2	2	1	3	

Table 4. P53 expression in Siewert-1 and Siewert-2 groups.

		Pattern of P53 espression				
		0	1	2	3	P value
P53 intensity	Siewert-3 (pts)	4	1	0	3	0.382284
	Siewert-2 (pts)	2	1	0	5	
P53 diffusion	Siewert-3(pts)	4	2	2	0	0.19487
	Siewert-2 (pts)	2	2	1	3	

Table 5. P53 expression in Siewert-3 and Siewert-2 groups.

		Pattern of P53 espression				
		0	1	2	3	P value
P53 intensity	Siewert-3 (pts)	4	1	0	3	0.612587
	Siewert-1 (pts)	2	1	1	3	
P53 diffusion	Siewert-3(pts)	4	2	2	0	0.231857
	Siewert-1 (pts)	2	1	2	2	

Table 6. P53 expression in Siewert-3 and Siewert-1 groups.

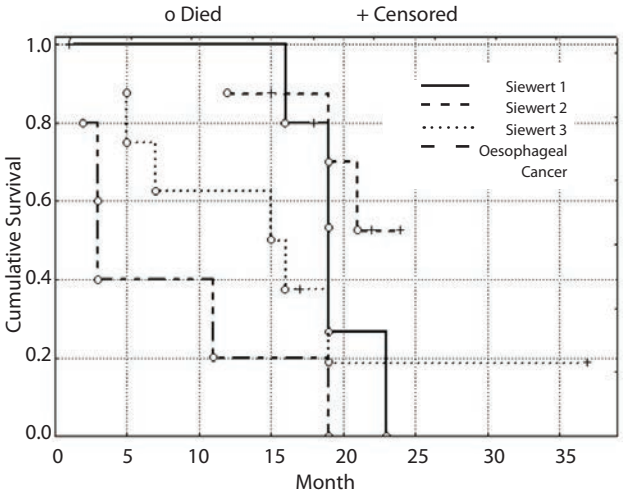

Figure 3. Kaplan-Meier survival of patients depends on cancer localisation. Median survival was higher in cardial than Oesophageal cancer (p=0.004), Siewert-II - 20 months, Siewert-I - 18 months, Siewert-II - 15 months, Oesophageal cancer - 3.3 months.

patients with precancerous lesions may be helpful for early detection of upper digestive tract tumours. New studies are required to assess

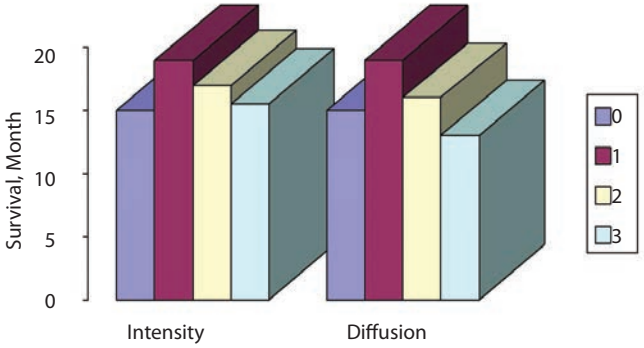

Table 7. Survival according to pattern expression of p53.

p53 expression profiling with detailed molecular genetic analysis to better understand disease pathogenesis and develop new diagnostic tools to improve the early upper gastrointestinal cancer diagnosis.

Acknowledgements

Dr. Tumak for her assistance in statistical evaluation. The author affirms no conflict of interest.

Upcoming Congresses and Meetings

International Liver Congress™ 2013

24 – 28 April 2013

Amsterdam, The Netherlands

Hosted by the European Association for the Study of the Liver (EASL), the International Liver Congress™ 2013 aims to bring attendees a programme packed with state-of-the-art basic science and the latest trial results in clinical medicine, as well as a range of educational opportunities through symposia, plenary lectures, and workshops among others. This programme continues to expand and improve and, this year, the EASL has added new sonography training for hepatologists sessions, as well as an extended Nurses and Associates Forum in response to feedback from attendees. Last year, the conference attracted a record number of participants, and this year's meeting looks set to be even bigger.

46th Annual Meeting of The European Society for Paediatric Gastroenterology, Hepatology and Nutrition

08 –11 May 2013

London, United Kingdom

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition is working in collaboration with The British Society of Paediatric Gastroenterology and Nutrition and the London Paediatric Gastroenterologists to bring you the 46th Annual Meeting of ESPGHAN. The scientific programme will offer the most recent updates in scientific and clinical research within the fields of paediatric gastroenterology, hepatology and nutrition. With stimulating key note lectures and symposia, sessions for postgraduates and allied health professionals combined with diverse satellite symposia from key industry partners, it promises to be a popular and exciting meeting. The theme for the Meeting is 'Research for a Better Future' which will include interesting topics such as Emerging concepts in parenteral nutrition, Coeliac disease and autoimmunity and Perinatal liver disease.

10th International Gastric Cancer Congress

19 – 22 June 2013

Verona, Italy

The International Gastric Cancer Association welcomes delegates to Verona for the 10th IGCC Congress. The congress features cutting edge research on a wealth of subject areas, including lymph node staging, molecular biology and gastric cancer, in formats including symposia, videos, paper and oral presentations, case conferences and panel discussions. The congress is also open to other specialist areas including oncologists and pathologists, and aims to encourage a multidisciplinary approach to gastric cancer.

12th World Organization for Specialized Studies on Diseases of the Esophagus (OESO) World Congress - Cancers of the Esophagus

27 – 30 August 2013

Paris, France

The OESO's goal is to bring together specialists from all disciplines involved in esophagology in order to carry out in-depth research which will contribute to the better care if patients, and the 12th OESO World Congress certainly encourages these aims. The congress returns to the theme of the first OESO event: 'The Intelligent Medicine', and both clinical and basic sciences will be at the forefront of the congress' discussions, with advancements in epidemiology, nutrition, endoscopy and mini-invasive surgery. The conference will also tackle a range of issues, with a focus on translating knowledge into cures. In keeping with the global focus of the congress, other organisations will also mark this event with their joint participations, including the IARC and the WHO with the UNESCO and the Académie Nationale de Chirurgie with several reputable cancer centres from all over the world.

International Liver Cancer Association (ILCA) 7th Annual Conference 2013

13 - 15 September 2013

Washington D.C, United States

In line with the ILCA's mission of advancing research in the pathogenesis, prevention, and treatment of liver cancer, ILCA 2013's programme will reflect a transversal and multidisciplinary, 'bench to bedside' approach, providing the ideal platform for scientific exchange, debate and networking of the highest quality. Clinical, translational and basic researchers, physicians and allied professionals across liver cancer related disciplines will convene to share best practices and findings and make ILCA 2013 the premier forum for advancing research in the pathogenesis, prevention, and treatment of liver cancer.

21st United European Gastroenterology (UEG) Week 2013

12 – 16 October 2013

Berlin, Germany

UEG Week is the largest and most prestigious GI meeting in Europe, and has developed into a global congress. The meeting makes use of a range of different formats, including live sessions, debates, tandem talks and video case sessions, to ensure that the up-to-date, cutting edge research is delivered in an exciting and engaging way.

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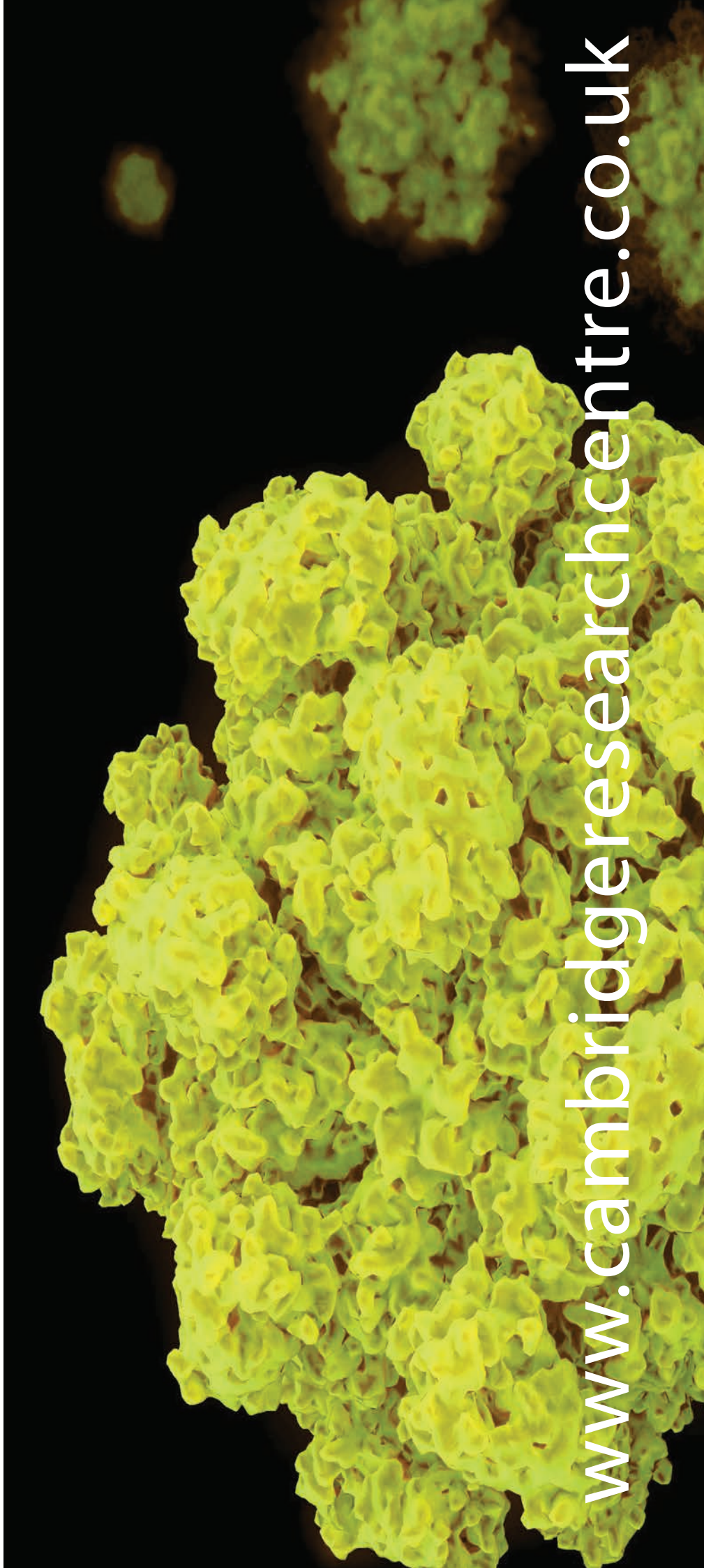

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