EMJ EUROPEAN MEDICAL JOURNAL

ONCOLOGY

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INSIDE

Review of the

European Cancer Congress 2013

Amsterdam, the Netherlands

ECCO-ESMO-ESTRO

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Treatment with TAFINLAR was proven to significantly extend progression-free survival (PFS) vs dacarbazine[1]

Efficacy in Previously Untreated Patients (BREAK-3 Trial)[1]		
	TAFINLAR (n=187)	Dacarbazine (n=63)
PFS Median, Months (95% CI)	**6.9** (5.2, 9.0)	**2.7** (1.5, 3.2)
Hazard Ratio (95% CI)	0.37 (0.24, 0.58) *P*<0.0001	

6.9 months
Median PFS with TAFINLAR

Investigator assessment, 25 Jun 2012, secondary data cutoff subsequent to primary data cutoff on 19 Dec 2011

The safety profile is based on data from 5 clinical monotherapy studies and included 578 patients with melanoma. The most frequently occurring adverse reactions (≥15%) of any grade for TAFINLAR included hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash, and vomiting.[1]

TAFINLAR can also cause serious, less common side effects, including increasing the risk of developing new primary cutaneous malignancies, serious febrile drug reactions, uveitis and iritis, and embryofoetal toxicity.[1]

discontinuation recommended if QTc increase is both >500msec and >60msec change from baseline. **Undesirable effects** Please refer to full SmPC before prescribing. *Very common*: papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, PPE syndrome, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills, asthenia. *Common*: cuSCC, seborrhoeic keratosis, skin tags, basal cell carcinoma, hypophosphataemia, hyperglycaemia, constipation, dry skin, pruritus, actinic keratosis, skin lesion, erythema, influenza-like illness, LVEF decrease. **Interactions** Avoid co-administration with strong inducers or inhibitors of CYP2C8 and CYP3A4, and agents that increase gastric pH, when possible. Exercise caution when co-administering with digoxin and with warfarin; consider additional INR monitoring. Dabrafenib may reduce efficacy of hormonal contraceptives; use alternative effective contraception and continue for 4 weeks post-discontinuation. **Pregnancy** Do not administer to pregnant women unless benefit to mother outweighs the risk to foetus. **Marketing authorisation (MA) nos.** EU/1/13/865/001; EU/1/13/865/003. **MA holder** GlaxoSmithKline Trading Services Ltd., Kinsale Road, Cork. **Legal category** POM. UK/MLO/0011a/13. July 2013.

Adverse events should be reported. Reporting forms and information can be found at: http://www.mhra.gov.uk/yellowcard
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Please see Summary of Product Characteristics for TAFINLAR.

Reference: 1. GlaxoSmithKline. TAFINLAR Summary of Product Characteristics.

TAFINLAR is not currently marketed in all territories and prescribers should check local marketing authorisation status before prescribing. Cost and reimbursement status may also vary.

GlaxoSmithKline

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Welcome

Kelly-Ann Lazarus

Editor, European Medical Journal

I am very excited to introduce to you our inaugural edition of *European Medical Journal – Oncology*. This journal gives a comprehensive review of the multidisciplinary European Cancer Congress (ECC 2013), an amalgamation of the European CanCer Organisation (ECCO), the European Society for Medical Oncology (ESMO), and the European Society for Therapeutic Radiology and Oncology (ESTRO). There is also a vast array of fascinating articles, reviews and analyses of treatment techniques provided by experts in the field of Oncology.

The Congress, held in Amsterdam, the Netherlands, saw over 18,000 delegates in attendance gathering to learn about key treatments of various types of cancer. An example of those highlighted include: wastage in radiotherapy dosage and the inadequacies in worldwide cancer care, with various different views on screening programmes throughout Europe.

Congress Chair and ECCO President, Cornelis van de Velde stated: "Thanks to this multidisciplinary collaboration, both oncology professionals and patient advocates will be able to see and learn from the tangible benefits of cancer disciplines working together, with active patient involvement placed at the heart of discussions."

Certain drugs were addressed that would improve the quality of life of many cancer patients, including both widely-used and unexpected medicines, such as ipilimumab, aspirin, cediranib, everolimus, and the anti-cancer drug T-DM1. In this edition, various novel therapies are discussed and authors explore treating pancreatic adenocarcinoma using intensity-modulated radiotherapy, a new radiotherapy technique, which has the potential to deliver a sufficient dose to the tumour whilst ensuring minimal dose to the surrounding critical structures. Researchers in a recent study also found that survival rates for head and neck cancer could be improved further by hyperfractionated radiotherapy.

In the future, the treatment of cancer is hoped to become unique from patient-to-patient, based on the molecular characteristics instead of purely the cancer location. New methods are also being assessed and researched for improvement of the lives of cancer patients and surviving patients, such as yoga as a treatment for insomnia among patients and survivors.

I hope that *EMJ – Oncology* provides a stimulating read and will act as a useful tool for easy access to any updates within the field of Oncology, throughout 2013 thus far.

Kelly-Ann Lazarus

Editor, European Medical Journal

For most metastatic colorectal cancer patients,

Treatment Goals Start with Survival

How can upfront treatment planning help your patients start—and stay—on a path to extended overall survival (OS)?

There are more treatment options than ever for patients with metastatic colorectal cancer (mCRC). For the majority of patients who are initially unresectable, extending OS remains the ultimate treatment goal.[1,2] And evidence now suggests that a simple treatment strategy involving multiple lines of therapy may be the optimal way to achieve it.[3,4]

Improved OS in mCRC correlates with the ability to receive all effective therapies during the course of disease.[5]

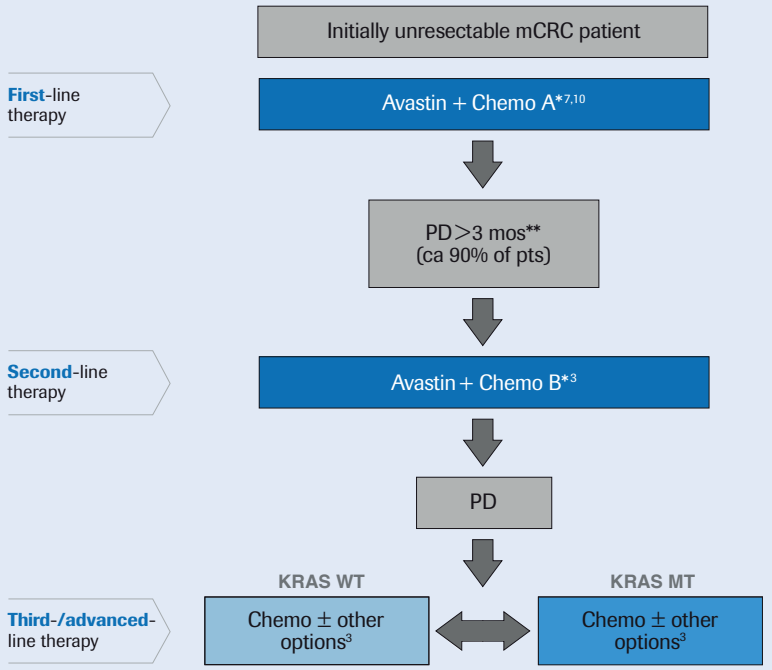
One clinically proven strategy to extend OS is starting with Avastin® (bevacizumab) plus chemotherapy and then switching chemotherapy—while maintaining Avastin at first progression.[3] Beyond extending OS, this strategy may allow for appropriate treatment sequencing through the continuum of care for improved patient outcomes.[3,4,6]

A new evidence-based treatment algorithm

At every step, your treatment decisions are based on robust, Phase III clinical data. Avastin is the only biologic supported by randomised, placebo-controlled Phase III pivotal studies to significantly improve OS in 1L, 2L, and beyond first progression.[3,7,8] The benefits of Avastin in terms of PFS and/or OS are achieved regardless of KRAS status and with a well-established safety profile in all patient populations, including those with comorbidities.[3,9]

For a simple treatment strategy to extend OS in initially unresectable mCRC, start with Avastin first line and continue beyond first progression.[3]

An evidence-based treatment algorithm[3,7,10-13]



*Clinical evidence suggests oxaliplatin- or irinotecan-based chemotherapy followed by maintenance therapy to progression.[3,7,14]

**And if no significant bevacizumab-related toxicity. If progressive disease (PD) is <3 months, therapy choice should be based on clinical judgement—as evidence in this clinical setting is not yet established.[3]

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Please see accompanying abbreviated prescribing information on following page.

References : 1. Adam R. *Ann Oncol.* 2003;14:ii13-ii16. 2. Teijido P, Gimeno T, Albors P. In: Cidon EU, ed. *The Challenge of Colorectal Cancer.* 2011. 3. Bennouna J, Sastre J, Arnold D. *Lancet Oncol.* 2013;14:29-37. 4. Arnold D, Andre T, Bennouna J, et al. Slides presented at: ASCO Annual Meeting; Chicago, Illinois; June 1-5, 2012. 5. Grothey A, Sargent D. *J Clin Oncol.* 2005;36:9441-9442. 6. Grothey A, Marshall L. *Oncology.* 2007:21:1-20. 7. Hurwitz H, Louis F, William N, et al. *N Eng J Med.* 2004; 350:2335-2342. 8. Giantonio B, Catalano P, Meropol N, et al. *J Clin Oncol.* 2007;25:1539-1544. 9. Hurwitz H, Yi J, Ince W, et al. *Oncologist.* 2009;14:1-7. 10. Genentech, Inc. Clinical Study Report: rhuMAb VEGF (Bevacizumab). South San Francisco, CA: Genentech, Inc; August 26, 2003. CSR AVF2107g. 11. Saltz L, Clarke S, Díaz-Rubio E, et al. *J Clin Oncol.* 2008;12:2013-2019. 12. Karapetis C, Khambata-Ford S, Jonker D, et al. *N Engl J Med.* 2008;359:1757-1765. 13. Grothey A, Van Cutsem E, Sobrero A, et al. *Lancet.* 2013;381:303-312. 14. Koopman M, Simkens L, Ten Tije A, et al. *J Clin Oncol*. 2013;31(15)(suppl):abstract 3502.

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PRESCRIBING INFORMATION

Refer to Avastin Summary of Product Characteristics (SPC) for full prescribing information. **AVASTIN® (bevacizumab) 25mg/ml concentrate for solution for infusion Indications:** In combination with fluoropyrimidine-based chemotherapy for treatment of metastatic carcinoma of the colon or rectum.

Dosage and Administration: Single use vials (25mg/ml bevacizumab) as 100mg/4ml or 400mg/16ml. Physicians experienced in antineoplastic medicines should supervise Avastin administration. *Recommended dose*: Continue until progression of underlying disease or until unacceptable toxicity. *Colorectal cancer*: either 5 mg/kg or 10 mg/kg every 2 weeks or 7.5 mg/kg or 15 mg/kg every 3 weeks. *Administration times; initial dose*: 90 minute IV infusion; *second dose*: 60 minute IV infusion if initial dose well tolerated; *subsequent doses*: 30 minute IV infusion if second dose well tolerated. Do not administer as IV push or bolus or mix with glucose. Dose reduction for adverse events not recommended. If indicated, discontinue or temporarily suspend therapy. Not recommended in children or adolescents. No dose adjustment in the elderly.

Contraindications: Hypersensitivity to bevacizumab, Chinese hamster ovary cell products, recombinant human or humanised antibodies or any excipients, Pregnancy, Lactation.

Precautions: In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient file. *Gastrointestinal (GI) and gall bladder perforation*; intra-abdominal inflammatory process may cause increased risk in metastatic colorectal cancer patients; permanently discontinue in patients developing GI perforation. *Fistulae*; permanently discontinue in tracheo-esophageal fistula or any Grade 4 fistula, consider discontinuation in non-GI fistula. *Wound healing*; do not initiate for at least 28 days following major surgery or until surgical wound has healed; withhold for elective surgery. *Necrotising fasciitis*; Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation; discontinue Avastin and initiate appropriate treatment promptly. *Hypertension*; control pre-existing hypertension prior to initiation. Diuretics not recommended for hypertension control with cisplatin. Monitor blood pressure during therapy and treat as per SPC: permanently discontinue if medically significant hypertension remains uncontrolled or for hypertensive crisis/encephalopathy. *Posterior Reversible Encephalopathy Syndrome (PRES);* should PRES develop, confirm by brain imaging, treat symptoms and discontinue Avastin. PRES signs include: seizures, headache, altered mental status, visual disturbance or cortical blindness with/without associated hypertension. *Proteinuria*; test prior to and monitor during treatment. Permanently discontinue if Grade 4 proteinuria (nephrotic syndrome) develops. *Arterial thromboembolism* including cerebrovascular accidents, transient ischaemic attacks and myocardial infarctions, especially if prior history or elderly: permanently discontinue if arterial thromboembolic events develop. *Venous thromboembolism* including pulmonary embolism; discontinue in Grade 4 thromboembolic events and monitor where Grade ≤3. *Haemorrhage, especially tumour-associated haemorrhage*; discontinue permanently if Grade 3/4. Caution in patients with congenital bleeding diathesis, acquired coagulopathy or during anticoagulant therapy. *Patients with CNS metastases*; monitor and discontinue treatment if intracranial bleeding occurs. *Congestive Heart Failure (CHF)*; caution in patients with clinically significant cardiovascular disease or pre-existing CHF. *Neutropenia*; fatal infection with or without severe neutropenia in combination with myelotoxic chemotherapy. *Hypersensitivity reactions/infusion reactions;* close observation recommended during and following bevacizumab administration. If a reaction occurs, discontinue infusion and administer appropriate medical therapies. Systematic premedication not warranted. *Osteonecrosis of the jaw (ONJ)*; has been reported. Consider dental examination and preventive dentistry before starting Avastin. Caution when Avastin and bisphosphonates are administered simultaneously or sequentially, avoid invasive dental procedures if possible. *Ovarian failure:* may occur. Consider fertility preservation strategies in women of child-bearing potential.

Drug Interactions: Risk of microangiopathic haemolytic anaemia (MAHA) when combined with sunitinib malate (50mg daily). Reversible on discontinuation of both agents. Infection with or without severe neutropenia (including some fatalities), mainly with platinum- or taxane-based therapies for metastatic or recurrent non-small cell lung cancer and metastatic breast cancer. Safety and efficacy with concomitant radiotherapy not established. EGFR monoclonal antibodies should not be administered in combination with Avastin in mCRC; risk of decreased efficacy and increased toxicity.

Pregnancy and Lactation: Contraindicated. No data on use in pregnancy; may inhibit foetal angiogenesis. Women of childbearing potential must use effective contraception during treatment and for 6 months after last dose. Discontinue breast-feeding during treatment and for 6 months after last dose.

Side-effects and Adverse Reactions: For full listings please refer to the Avastin SPC. *Serious reactions, very common*: Leucopenia, thrombocytopenia, neutropenia and febrile neutropenia. Peripheral sensory neuropathy. Hypertension. Diarrhoea, nausea, vomiting. Venous thromboembolic events. Asthenia, fatigue. *Serious reactions, common*: Anaemia. Sepsis, abscess, infection. Dehydration. Cerebrovascular accident, syncope, somnolence, headache. Supraventricular tachycardia, CHF. Arterial thromboembolism, deep vein thrombosis, haemorrhage, including pulmonary haemorrhage. Pulmonary embolism, dyspnoea, hypoxia, epistaxis. Ileus, intestinal perforation and obstruction, abdominal pain, GI disorder, stomatitis. Palmar-plantar erythrodysaesthesia syndrome. Muscular weakness, myalgia, arthralgia. Proteinuria, urinary tract infection. Pain, lethargy, mucosal inflammation. Dysphonia. *Serious reactions, uncommon/ rare/very rare*: Fistulae. PRES (with or without associated hypertension). Necrotising fasciitis. Hypertensive encephalopathy. *Serious reactions (frequency not known)*: pulmonary hypertension, nasal septum perforation, renal thrombotic microangiopathy which may clinically manifest as proteinuria with or without concomitant sunitinib use, gastrointestinal ulcer, hypersensitivity/infusion reactions with possible co-manifestations: dyspnoea/difficulty in breathing, flushing/redness/ rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting, ONJ, gall bladder perforation. *Other, very common*: Wound healing complications. Anorexia. Dysgeusia, dysarthria. Eye disorder, lacrimation increased, rhinitis. Rectal haemorrhage, constipation. Ovarian failure. Exfoliative dermatitis, dry skin, skin discolouration. Pyrexia. Any of the above may become serious. Elderly; increased risk of severe leucopenia and thrombocytopenia; neutropenia, nausea, headache, diarrhoea, fatigue, or arterial thromboembolic events. Laboratory abnormalities – refer to SPC. **Legal Category:** POM **Presentation and Basic NHS Cost:** Pack of one 100mg vial: £242.66. Pack of one 400mg vial: £924.40. Excluding VAT

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Foreword

Prof Bill Heald, CBE

The Colorectal Cancer Unit,
Champalimaud Foundation for the Unknown, Lisbon, Portugal.
2013 ESSO Lifetime Achievement Award

Welcome to the first edition of Oncology for the *European Medical Journal*. It is with great enthusiasm I introduce this as it coincides with exciting personal events and dramatic changes to the treatment of colorectal cancer. I was invited to join and help shape a new unit; the Colorectal Cancer Unit at the Champalimaud Foundation, Lisbon, Portugal, which raised a great opportunity and influenced my questioning, 'What part of current practice around the world is in need of a revolution?'

For 60 years, surgeons, pathologists, radiologists, and their friends in the industry have contemplated the challenges and detail of preserving the anal sphincters in rectal cancer surgery. Fundamental to this, an observation by Basil Morson of St. Marks Hospital, that "the palpable lower edge of a rectal cancer is most invariably the microscopic lower edge." In other words, malignant spread down the anorectal wall, as occurs in gastric and oesophageal cancer, is rare.[1] In more than 90% of rectal cancer cases there is no cancer in the pelvic floor or anal sphincters – the continence mechanism is truly cancer-free. "In the surgical world the arbitrary '5 cm rule' was abandoned long ago[2] and it became possible to make the widely dreaded permanent colostomy, a comparative rarity…in many centres, including Basingstoke, it was reduced from 70% to well below 10%."[3]

With the new century, came the radiotherapy revolution and then chemo-radiotherapy, a disastrous 'toxic mix' when combined with low anorectal anastomosis. With little serious attempt being made to spare the continence mechanism the addition of standard radiation has increased 'toilet-dependent' patients from 6% to 30% and doubled those with "any incontinence."[4] Approximately one half of those undergoing this 'toxic mix' have seriously restricted lives.[4]

With this background my first question to the Professor of Radiotherapy at Champalimaud was about anal sparing, which is already achievable with many RT machines around the world.[5,6] With the Varian EDGE Image guided machine (IGRT) at Champalimaud, Prof Carlo Greco was able to say that it is "particularly easy."[7] Questions may remain in the radiotherapy world if muscle sparing implies also missing part of the most distal mesorectum. However recent Pelican Mercury data suggest that the subsequent Total Mesorectal Excision (TME) will make this omission insignificant - i.e. there is no need to irradiate tissue that is to be excised.[8,9]

Then suddenly, a revolutionary discovery was made. Surely, with modern specialist MRI, the MDT discussion should occur before any treatment and address together both "anal sparing from irradiation" at the same time as "surgical sphincter preservation." No longer, anywhere in the world, should oncologists of any hue prescribe RT or CRT until a joint decision has been made by surgeon, radiologist, and radiation oncologist together.

This journal contains informative reviews from the 2013 European Cancer Congress, (ECCO2013), whose central theme was multidisciplinarity and which shared decisions on preserving function, with visual representation of radiation dosage to all retained tissues, will give new meaning and vitality to every MDT. New research was presented that could potentially add 10 years to the lives of advanced melanoma patients if treated with a particular antibody. Radiotherapy dosage was discussed and the need for screening for colorectal cancer throughout Europe was emphasised. It is thus with pleasure I introduce the first of many in the *EMJ – Oncology* volumes.

Prof Bill Heald

The 2013 ESSO Lifetime Achievement Award was presented to Professor Bill Heald in recognition of the dedication of his professional life to the research and development of the Total Mesorectal Excision (TME) technique for rectal cancer. His Award lecture was entitled: '2013, a year of challenges in the technique of TME'.

1. Basil Morson, Personal communication, St. Mark's Hospital, London, UK, 1985.

2. Williams NS et al. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival. Br J Surg. 1983;70(3):150-4.

3. Heald RJ et al. The Basingstoke Experience of Total Mesorectal Excision 1978-1997. Arch Surg. 1998;133(8):894-8.

4. Kornmann M. The risk of radiotherapy- late side effects. Presented at ECCO 2013.

5. Temple LK et al. The impact of radiation on functional outcomes in patients with rectal cancer and sphincter preservation Semin Radiat Oncol. 2003;13(4):469-77.

6. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ. 2006;333:779.

7. Chand et al. Lymph node status does not predict local recurrence in the TME era. Dis Colon Rectum. 2013.

8. Syk E et al. Local recurrence in rectal cancer: anatomic localization and effect on radiation target. Int J Radiat Oncol Biol Phys. 2008;72(3):658-64.

9. Sarah Roels et al. Definition and delineation of the clinical target volume for rectal cancer. Int. J. Radiat Oncol Biol Phys. 2006;65(4):1129-42.

ECC CONGRESS 2013

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27TH SEPTEMBER-1ST OCTOBER 2013

Welcome to the *European Medical Journal* review of the European Cancer Congress 2013

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Welcome to the *European Medical Journal* review of the European Cancer Congress 2013

Introduction to the 17th ECCO, 38th ESMO, and 32nd ESTRO European Cancer Congress

A COMBINATION of the European CanCer Organisation (ECCO), the European Society for Medical Oncology (ESMO), and the European Society for Therapeutic Radiology and Oncology (ESTRO) was always going to be an awe-inspiring event, and this year's European Cancer Congress (ECC 2013) well and truly delivered.

At a time when the threat of cancer continues to grow, experts predict that the number of people diagnosed with cancer worldwide will rise to 21.3 million in 2030, with over 13.1 million dying from the disease. The need for a figurehead to lead the fight for oncological healthcare is clear, and the ECC is stepping up to the task at hand.

Formed in 2007 to replace the Federation of European Cancer Societies (FECS), the non-profit organisation now represents over 60,000 cancer professionals, including six founding members and 24 member societies. Every 2 years since 1983, the conference has continued to promote the need for a multidisciplinary approach to cancer care, successfully evolving into what is considered to be Europe's premier cancer meeting.

The Congress received the highest number of abstract submissions yet, with 3,176 regular abstracts and 121 late-breaking abstracts. As seen in this Congress Review section, Europe-wide issues were prominent in the Congress, personified by the proposal of a new financing model to tackle major disparities in cancer treatment, the *State of Oncology Report 2013*, as well as 'irrefutable' evidence that colorectal

> "The ECC 2013 is truly the largest platform for showcasing the latest developments in practice-changing studies of new and significant scientific importance in Europe."
>
> *Prof Cornelis van de Velde, Congress Chair, ECCO President*

cancer screening programmes across the continent would result in a fall in death rates.

Presentations of note also mentioned within our comprehensive summary include the potential negative outcomes linked to routine prostate specific antigen (PSA) tests, while the subject of radiotherapy was cast under intense forward-thinking scrutiny, with news that a significant part of the daily radiotherapy curative dose is 'used up' in compensating for tumour growth.

"The ECC 2013 is truly the largest platform for showcasing the latest developments in practice-changing studies of new and significant scientific importance in Europe, and for bringing cutting-edge data to Europe," Prof Cornelis van de Velde, the Congress Chair and ECCO President, wrote in his welcoming article.

"Attending congresses and meetings remains an important key opportunity for oncology professionals for networking and ensuring they are up-to-date on the latest data and techniques, and means of research, treatment, and care."

At a time when Europe saw 3.4 million new cases and 1.8 million cancer-related deaths in 2012 alone, the branch of oncology is proving to be more essential than ever. But after observing ECCO's commitment to ensuring that current and future patients benefit from the latest medical innovations and care, it is clear the future is in safe hands.

Report condemns current worldwide cancer care

> "It's bad to have cancer, and worse to have cancer if you are poor. The gap between rich and poor, highly educated and least educated, and the north-south divide is substantial and continuing to grow."
>
> *Prof Peter Boyle, President, International Prevention Research Institute, Lyon, France*

A NEW financing model proposal, created to tackle major disparities in the prevention, diagnosis, treatments, and outcomes of cancer worldwide, was presented at ECC 2013 on Monday 30th September.

Presented by the President of the International Prevention Research Institute, Prof Peter Boyle warned that radical solutions are required in regards to access to treatment, with the present economic model currently in a broken and unequal state.

The report, named the '*State of Oncology Report 2013*', is based on the opinions of over 100 eminent medical scientists who describe the state of oncology in over 50 countries.

"Many parts of the world are already unable to cope with the current situation and are totally unprepared for the future growth of the cancer problem," Prof Boyle said. "It's bad to have cancer, and worse to have cancer if you are poor. The gap between rich and poor, highly educated and least educated, and the north-south divide is substantial and continuing to grow.

"Radical solutions are urgently needed: the status quo is not an appropriate response to the current situation. It should be recognised that no single source of philanthropy has the means to solve this problem, and that new models are needed to cope with and improve this situation."

The rise in world population is believed to soon play a major part in the rise of cancer burden, particularly in countries such as India, China, and Nigeria. The United Nations estimates that India and China will each have a population of 1.45 billion by 2028, while Nigeria will be larger than the USA by 2050.

"Given the scale of the need to deal equitably with cancer worldwide, working to improve health must cease to be viewed as a competition. Public and private organisations have an underlying suspicion of each other that must be overcome in the interests of improving global cancer care and outcomes," Prof Boyle concluded.

Ipilimumab can increase survival rates in melanoma patients

ADVANCED melanoma patients can survive up to 10 years if they have been treated with a monoclonal antibody, ipilimumab, it was announced at ECC 2013. This is based on the largest study of the survival rates in these patients.

Prof Stephen Hodi, Assistant Professor of Medicine at the Dana-Farber Cancer Institute, Boston, USA, said: "Our findings demonstrate that there is a plateau in overall survival, which begins around the third year and extends through to the tenth year."

> "Our findings demonstrate that there is a plateau in overall survival, which begins around the third year and extends through to the tenth year."
>
> *Prof Stephen Hodi, Dana-Farber Cancer Institute, Boston, USA*

Ipilimumab is a human monoclonal antibody, which targets a protein receptor called Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4). This protein receptor is inhibited from recognising and destroying melanoma cancer cells, so ipilimumab switches off the inhibitory mechanism allowing CTLA-4 to continue killing cancer cells.

It was known that some patients treated with the drug survived for long periods, with one Phase III clinical trial having an 18% survival rate after 5 years. Prof Hodi and colleagues collected data on 1,861 patients to estimate the drug's effect on long-term survival. Additionally, data from 2,985 ipilimumab patients who were not part of any clinical trial, gave the researchers a total of 4,846 patients.

The analysis of data from the first cohort of patients showed that the overall median survival was 11.4 months. According to Prof Hodi, 254 patients (22%) were still alive after 3 years, with no deaths occurring after 7 years, at which time the overall survival rate was 17%. Data from the combined group of patients showed that the median survival was 9.5 months, with 21% survival rate after 3 years.

Prof Hodi concluded: "The limitation of this study is that it is a pooled analysis from Phase II, Phase III, and observational data, and not from a single randomised, controlled study. However, these results are consistent with our findings from randomised clinical trials and confirm the durability of the plateau in overall survival, previously shown to extend to at least 5 years but now shown to extend up to 10 years."

Radiotherapy dosage wasted in compensating between treatments

THE DAILY dose of radiotherapy could be wasted in compensating for cancer cell growth that occurs overnight and during weekends in early breast cancer patients, according to research presented at ECC 2013.

Prof John Yarnold, Professor of Clinical Oncology at the Institute of Cancer Research, London, UK, said: "Traditionally, breast cancer has not been regarded as a fast growing cancer, unlike some other cancer types, but our research now suggests that a significant part of the daily radiotherapy curative dose is 'used up' in compensating for tumour growth overnight and over weekends."

> "This suggests that a shorter 1 week radiotherapy schedule, replacing the 5 to 7 week schedules that were more usual in the past, may be more effective against breast cancer recurrence and reduce the chances of side-effects on the surrounding normal tissues."
>
> *Prof John Yarnold, Institute of Cancer Research, London, UK*

Research carried out by Prof Yarnold and Ms Jo Haviland, a senior statistician at the Institute of Cancer Research's (ICR) Clinical Trials and Statistics Unit (CTSU), London, UK, was based on the Standardisation of Breast Radiotherapy (START) trials (START Pilot, START A and START B). Since 1986, this study has been evaluating the effects of shorter radiotherapy schedules after surgery for early breast cancer patients.

Data from 5,861 UK patients were utilised and placed into the three categories of the START trials. The START Pilot and START A trials compared the international standard of 50 Gray (Gy) in 25 daily doses of 2.0 for a 5 week duration, contrasted with two other schedules of slighter higher daily doses of 3.0-3.3 Gy over the same time frame. START B trial compared the international standard with slightly lowered parameters, giving 40 Gy in 15 daily doses of 2.67 Gy over a 3 week duration. It was observed that after a 10 year follow-up, the 3 week schedule was just as beneficial as the 5 week counterpart in cancer prevention. With regards to safety, the 3 week schedule was gentler on normal tissues, with fewer late side-effects, compared with the 5-week schedule. These data found that approximately 0.60 Gy of daily radiotherapy is wasted during the 5-week duration to compensate for cancer cell growth.

Prof Yarnold said: "This suggests that a shorter 1-week radiotherapy schedule, replacing the 5 to 7-week schedules that were more usual in the past, may be more effective against breast cancer recurrence and reduce the chances of side-effects on the surrounding normal tissues."

Diabetics beware: increased risks of breast and colon cancer

DIABETIC patients have an increased risk of developing breast and colon cancer and also have a greater risk of dying from the diseases, according to a meta-analysis.

Dr Kristin De Bruijn, a PhD student in the Study Department at the Erasmus University Medical Center, the Netherlands, and colleagues, were involved in 20 trials which included more than 1.9 million patients with breast or colon cancer, with or without diabetes.

The results found that there was a 23% increased risk of diabetic patients developing breast cancer, as well as a 38% increased risk in dying from the disease compared to non-diabetic patients. For colon cancer, diabetic patients had a 26% increased risk of developing the disease, while 30% of diabetics had an increased risk of dying from the disease compared to their non-diabetic counterparts.

"The results for breast and colon cancer incidence in patients with diabetes are consistent with other meta-analyses," Dr De Bruijn said. "Cancer patients who are obese and diabetic are an already more vulnerable group of individuals when it comes to surgery, as they have an increased risk of developing complications both during and after surgery. If more obese and diabetic patients have to have an operation because of cancer, health costs will increase."

Prof Hans-Joerg Senn, Scientific Director at the Tumor and Breast Centre ZeTuP, St. Gallen, Switzerland, said: "The message from the Erasmus Medical Center is disturbing and highly important, for the medical community, as well as for the public and politicians. It highlights once more the importance of negative interactions between lifestyle, metabolism, overweight, and certain frequent types of cancers, such as here between diabetes, obesity, and breast cancer as well as colon cancer. It is time for increased and more effective information and prevention campaigns, especially in the economically developed world, where caloric abundance is prevalent."

The follow-up research from Dr De Bruijn and colleagues will focus on what effects other factors associated with diabetes have on cancer risk and death, such as the antidiabetic medication, metformin, as well as insulin, and the overall duration of diabetes.

"Cancer patients who are obese and diabetic are an already more vulnerable group of individuals when it comes to surgery... If more obese and diabetic patients have to have an operation because of cancer, health costs will increase."

Dr Rui Quintas,
Istituto Neurologico Carlo Besta, Italy

Need for colorectal screening programmes throughout Europe

COLORECTAL cancer (CRC) screening in Europe is highly effective in reducing mortality from the disease, and priority should be placed on early detection.

The report on results extracted from the Survey of Health, Ageing, and Retirement in Europe (SHARE) project was presented by Prof Philippe Autier, Vice President of Population Studies at the International Prevention Research Institute, Lyon, France. The findings shed light on the exposure to screening in men and women aged 50 and over, in 11 European countries between 1989 and 2010. The cause of death database from the World Health Organization (WHO) was utilised to calculate the changes in the death rates from CRC in different countries, in relation to their screening practices.

Screening can either involve a faecal occult blood test (FOBT) or an endoscopic examination of the bowel to look for polyps, which are cancer precursors. "We saw quite clearly that the greater proportions of men and women who were screened, the greater the reductions in mortality," Prof Autier said. "Reduced death rates from CRC were not noticeable in countries where screening was low, even though healthcare services in those countries were similar to those in countries where screening was more widespread."

> "We saw quite clearly that the greater proportions of men and women who were screened, the greater the reductions in mortality."
>
> *Prof Philippe Autier, Vice President of Population Studies, International Prevention Research Institute, Lyon, France*

In the countries studied, there was a 73% decrease in CRC mortality over a period of 10 years in men, and an 82% reduction in females, possibly due to having one or more endoscopic examinations. Prof Autier remarked: "The evidence could not be clearer, and it is therefore very disappointing that national differences in the availability of CRC screening programmes are still so pronounced."

According to Prof Autier and fellow researchers, these factors can be attributed to lack of national CRC screening programme, the acceptability of screening methods which is often due to cultural differences, and absence of qualified personnel. Analysis of a larger cohort of data in a wider range of countries is next on the agenda for the research team.

Aspirin improves colon cancer survival

A CELL-SURFACE protein could potentially be used to predict whether or not colon cancer patients may benefit from taking aspirin.

According to data presented at the ECC 2013, it was found that the salicylate drug improves the outcomes in patients whose tumour cells express human leukocyte antigen class I (HLA class I), a protein produced by a collection of genes involved in the functioning of the immune system.

Dr Marlies Reimers, a PhD student in the Department of Surgery, Leiden University Medical Center, the Netherlands, and colleagues found that patients suffering from tumours expressing HLA class I, when taking 80 mg of aspirin daily, were half as likely to die during the average 4 years of follow-up.

Previous research has shown that taking a low dose of aspirin after being diagnosed with colon cancer can improve a patient's outcome, though the reasons are unknown. However, the new findings suggest this may be due to the effect of aspirin on platelets, cell fragments in the blood involved in clotting, and the subsequent interaction with the body's immune system.

Dr Reimers said: "We think that platelets are involved in cancer spreading to other parts of the body by shielding tumour cells in the bloodstream so that they cannot be recognised by the immune system and can finally colonise distant organs.

"Aspirin could help to 'unmask' those tumour cells by attacking platelet formation, so that the immune cells can detect and eliminate them."

Studying 999 tumours and extracting DNA from 663 tumours respectively, researchers used tissue microarray technology to investigate the pattern of protein expression in known aspirin-using colon cancer patients, who were registered with the Eindhoven Cancer Registry between 1998 and 2007.

"Although speculative, it may be that the interaction of platelets with HLA-positive tumour cells circulating in the blood promotes the metastatic potential of these cells," said Dr Reimers. "Aspirin interferes with this interaction, thereby decreasing the risk of metastatic disease and colon cancer-related death."

Though it is agreed more data are required, randomised clinical trials have started in both the UK in Asia.

"Aspirin could help to 'unmask' those tumour cells by attacking platelet formation, so that the immune cells can detect and eliminate them."

Dr Marlies Reimers,
Leiden University Medical Center,
the Netherlands

PSA screening does more damage than good

MEN experience more harm than benefits resulting from routine prostate specific antigen (PSA) tests.

The examination is used throughout Europe to check for prostate cancer, despite no organised, population-based screening programme, and a lack of evidence supporting PSA utility.

Prof Mathieu Boniol, Research Director at the International Prevention Research Institute (iPRI), Lyon, France, presented these findings, suggesting that the test should be used as an additional aid in diagnosing cancer, rather than the main entry point.

"The harm from routine PSA testing can have a serious effect on the quality of life of patients and provides additional evidence against the use of organised screening for prostate cancer," he said.

In order to create a virtual population of 2,000 men, researchers combined results from the European Randomised Study of Screening for Prostate Cancer (ERSPC), extracting data on the number of men requiring a prostate biopsy and the number of prostate cancer cases diagnosed, with other published data on side-effects associated with biopsies and surgeries used to remove prostate tumours.

Results revealed relatively similar death rates, estimating 5.17 deaths due to prostate cancer in the unscreened group, compared to 4.1 deaths in those who underwent PSA tests.

However, in order to prevent a single death from prostate cancer in the 1,000 men screened, numbers of biopsies doubled with 154 additional prostate biopsies, on top of 35 additional prostate cancers diagnosed, 12 more cases of impotence, and a further three cases of incontinence would occur.

"This national study indicates that it causes more harm than good, especially in men aged 70 or older who have triple the risk of younger men of dying after the operation," President of ECCO, Prof Cornelis van de Velde, said. "These results should lead to stricter guidelines and registries to evaluate the over-treatment of prostate cancer."

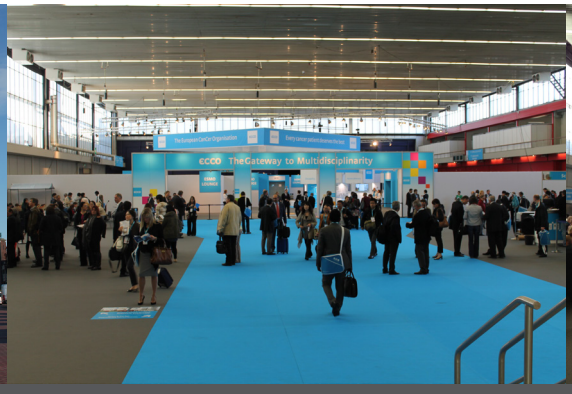
Younger patients are at higher risk of detrimental effects of colorectal cancer

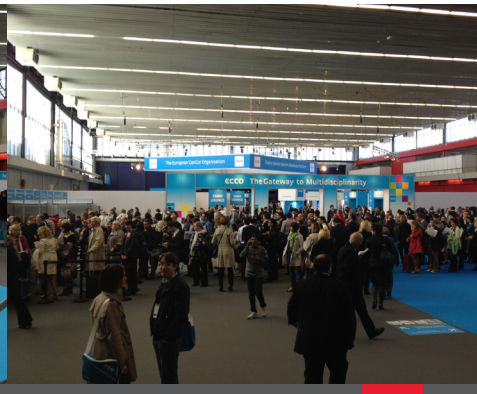
YOUNG patients with colorectal cancer that has metastasised to other parts of the body represent a high-risk group due to their low response to anti-cancer treatments. It was also shown that this group has a greater risk of death in comparison with other age groups.

The investigation consisted of 20,034 patients in 24 Phase III clinical trials for colorectal cancer; 695 patients (3%) were younger than 40 years old. The results showed that the youngest and oldest groups had the highest risk of disease progression in comparison to middle-aged patients. The youngest patients had a 30% increased risk of dying from the disease, when compared with 57-year-olds. The youngest group also had a 28% increased risk in dying when compared with 61-year-olds. The older population of patients had a 72% increased risk of death and 19% increased risk of metastasis, when compared to 57 and 61-year-olds in the follow-up procedures.

Dr Christopher Lieu, an Assistant Professor at the University of Colorado, USA, said: "The reasons why the incidence is increasing in younger patients remain unknown, although genetic predisposition, environmental factors, fewer early cancer detection in this population, or a combination of these factors are thought to play a role.

"We carried out this study to see whether age was associated with time until cancer progresses or the patient dies. We also wanted to get a better picture of the age-response relationship and identify how risk changes as people age, rather than simply comparing one group (patients younger than 40) with another group (patients older than 40)."





New combination therapy used to treat glioblastoma

A NEW approach for treating a particularly aggressive brain tumour, glioblastoma, has been discovered, as well as a potential new biological marker which can predict the tumour's response to treatment.

Prof Wolfgang Wick, Chairman of the Neuro-Oncology Programme at the National Centre for Tumour Diseases, and a Professor of Neuro-Oncology at the University of Heidelberg, Germany, said: "Glioblastoma is a very aggressive, fast-growing tumour that shows an infiltrative growth, making local therapies of very limited efficacy. The tumour is also resistant to all current chemotherapy treatments, and has devastating effects on the quality of life of patients."

The combination of radiotherapy with an anti-cancer drug called APG101 (a fusion protein similar to an antibody), blocks a cell-signalling pathway called CD95 that plays a critical part in cancer development.

A randomised Phase II study involving 84 glioblastoma patients, who had already received initial treatment such as radiotherapy and whose cancer had recurred, were categorised into those who received either radiotherapy alone or radiotherapy with an intravenous dose of 400 mg of APG101 once a week.

The results showed that 21% of patients who were treated with combination therapy were still alive after treatment, in comparison with the 4% that were treated with just radiotherapy alone. After 2 years, there were more people alive who underwent the combination therapy (22%) than those who did not (7%).

Prof Wick commented: "It was already known that APG101 might be an innovative approach for treating glioblastoma, but the size of the protein molecule was potentially too large to cross the protective blood-brain barrier and target the tumour. Radiotherapy opens up this barrier and may therefore be an effective vehicle for this compound."

Further studies have shown that APG101 plays a major role in the blocking of CD95/CD95 ligand (CD95L) system. CD95 is a cell surface receptor protein and it is bound to CD95L, which induces cell death. But further research had shown that this made cancer cells resistant to cell death. Consequently, patients with tumours expressing CD95L had a worse prognosis than those with tumours who did not express it, but these patients respond better to APG101 combination treatment. It is hinted by Prof Wick that CD95L could be one of the first predicative markers in neuro-oncology.

Paving the way for personalised treatments

THE PERSONALISATION of cancer care, where treatment is catered based on the molecular characteristics instead of their location was presented at the ECC 2013.

Dr Christophe Le Tourneau, Head of the Phase I Programme at the Institut Curie, Paris, France, presented the findings of the SHIVA trial. This trial is the first randomised trial to use drug treatments based on the molecular profile of the patient's tumour. It is also the first trial to examine this therapy on all tumour types. Dr Le Tourneau also mentioned that 40% of the molecular abnormalities already have targeted treatment.

So far, 320 patients were included in this trial, with 60 participants comprising of the standard group that received chemotherapy. The profile of the patients that took part in the trial had recurrent or metastatic cancer and were unresponsive to treatment.

The researchers focused on obtaining a biopsy of the metastasis, since the molecular profile of the primary tumour may not be the same as those that have metastasised. The parameters of the investigation included the availability of tumour samples, proportion of patients for which the necessary analyses could be undertaken, the possible identification of molecular abnormality, and the existing corresponding therapy and time frame for the creation of the tumour profile.

> "At present we have no data on the efficacy of drugs in patients with the same molecular abnormality but different tumour types."
>
> *Dr Christophe Le Tourneau, Institut Curie, Paris, France*

Molecular targeted agents work in the presence of their corresponding targets, allowing for diminished side-effects and an increase in efficiency. So far drugs that have been developed were based on the primary location and histology of the tumour. This meant that there were many potentially promising targeted drugs which failed in the early clinical trials as they did not induce a response in a sufficient number of patients.

Dr Le Tourneau said: "At present we have no data on the efficacy of drugs in patients with the same molecular abnormality but different tumour types." Dr Le Tourneau continued to say that the therapy will be dependent on several molecular abnormalities instead of one entity, adding that the tumour biology will be a deciding factor in which target agents will be developed.

European initiative to improve oesophageal and gastric outcomes

LARGE variations between European countries in patient survival after surgery for oesophageal and gastric cancers are apparent, though the reasons for these are unclear.

It is known that hospitals which treat the highest numbers of patients for a wide variety of diseases tend to have a greater expertise, resulting in a better overall outcome for patients. This, however, may not be the full picture. Dr Johan Dikken, a surgical resident at Leiden University Medical Center and the Medical Center Haaglanden, the Netherlands, told those who attended the congress that European cancer surgeons have launched a new initiative - the European Upper GI Cancer Audit (EURECCA Upper GI), which aims to discover the reasons for the differences between countries.

The focus of the investigation was to observe survival rates 30 days after surgery in relation to volume of operations carried out at each hospital in the Netherlands, Sweden, Denmark, and England. The pilot study carried out between 2004 and 2009, scrutinised the outcomes after 10,854 surgical operations for oesophageal cancer, and 9,010 operations for gastric cancer.

The pilot study found that the death rates 30 days after surgery were lower after oesophagectomy (4.6%) than gastrectomy (6.7%), but the variation between countries was considerable. For example, Sweden had the lowest death rate after oesophagectomy (1.9%) while England had the highest (5.8%). For gastrectomy, the death rate was significantly higher in the Netherlands (6.9%) than in Sweden (3.5%) and Denmark (4.3%).

With reference to the volume of surgical operations, the results showed that hospitals with the highest volumes (over 30 procedures a year) tend to have lower death rates, but there were significant variations between countries. In Denmark, 65.6% of oesophagectomies were performed in hospitals carrying out 30 procedures a year, whereas in Sweden a similar proportion (63.6%) of operations, were performed in hospitals carrying out less than 11 procedures a year.

Dr Dikken concluded: "The goal of the EURECCA project is to improve patients' outcomes throughout Europe by comparing and analysing care between countries and hospitals in order to discover what are the key factors that make a difference."

Anti-cancer drug T-DM1 may benefit women with advanced breast cancer

COMBINATION drug, T-DM1 has shown significant improvements in delaying the progression of breast cancer in women with advanced HER2 positive breast cancer whose cancer has returned or progressed in spite of the use of previous treatments.

Prof Hans Wildiers, from the University Hospital Gasthuisberg, Belgium, said: "This study shows that even in heavily pre-treated woman, 75% of whom had cancer that has spread to the internal organs, T-DM1 nearly doubles progression-free survival – the length of time before disease progression or death, whichever occurs first – compared to standard therapy, and with a more favourable safety profile. Few drugs have been able to achieve both improved progression-free survival and a better toxicity profile. These results indicate that this drug has important clinical benefits for patients."

A conjugated monoclonal antibody, T-DM1 is the combination of trastuzumab, and the cell-killing drug emtansine (DM1) which targets and kills breast cancer cells that have large amounts of HER2 on their cell surfaces (known as HER2 positive breast cancer). This drug has shown to benefit breast cancer patients with metastases and those treated with trastuzumab and taxane-based chemotherapy.

TH3RESA, an international Phase III clinical trial, recruited breast cancer patients whose cancer was inoperable and had recurred or metastasised after treatment intervention. In the study, 602 patients were randomised into two groups to either receive 3.6 mg/kg via intravenous infusion of the drug every 3 weeks, or undergo a treatment plan recommended by their physician's choice (TPC). Approximately 75% of the participants had visceral disease and received on average four previous treatments excluding single agent hormonal therapy.

The results showed progression-free survival increased by nearly 3 months, from 3.3 months for TPC patients to 6.2 months for T-DM1 patients. 31.3% of T-DM1 patients showed response to the T-DM1 drug in comparison to 8.6% of the TCP group. Overall, patient survival showed a similar trend but this did not reach a significant level to validate the benefits of the T-DM1 treatment.

Prof Wildiers concluded: "This trial will continue until the final overall survival analysis takes place or until the survival benefit for treatment with T-DM1 reaches statistical significance at an interim analysis."

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Hyperfractionated radiotherapy improves survival in head and neck cancer patients

PATIENTS with locally advanced head and neck cancers can benefit from the use of an intensified form of radiotherapy, which has shown increased survival rates when compared with standard radiation therapy.

A meta-analysis, which included 11,000 patients across many countries in Europe and North America, as well as Brazil and other developing countries, was undertaken in an international collaboration known as MARCH. Altered fractionation radiotherapy (AFRT) was compared with standard fractionation radiotherapy (SFRT), the results showing an 8% reduction in the risk of death in the AFRT group, as well as a 9% reduction in the risk of progression or death.

Dr Pierre Blanchard, a radiation oncologist from the Institut Gustave Roussy, Villejuif, France, reported that although the standard care method should remain concomitant chemoradiation (CRT), which requires both radiotherapy and chemotherapy to be administered together, to treat local advanced head and neck squamous cell carcinomas, AFRT should be utilised when treatment intensification is required, and when CRT is not appropriate due to the presence of other pre-existing conditions such as cardiac and renal disease.

There are various schedules in which AFRT can be given. The first is hyperfractionation where radiotherapy is given twice a day for 10 days to a total dose of approximately 80 Grays (Gy), compared with the dose of 70 Gy under the SFRT regime. The second schedule involves reducing the overall treatment time but the dosage is kept at the same level or at a slightly lower dose. There are increased acute side-effects with AFRT, while SFRT is mainly characterised as having late side-effects.

Dr Blanchard said: "After more than 7 years patient follow-up, our research has shown that the higher dose intensity of AFRT works to improve outcomes. The hyperfractionated regime is the most effective in terms of overall survival. Indeed, in this group of trials the risk of death is reduced by 18% by the use of hyperfractionated radiotherapy, with 41% of patients alive at 5 years compared to 33% in the SFRT group."

Dr Blanchard concluded: "By carrying out a large-scale analysis such as this one, we believe that we have provided enough evidence to indicate that doctors should recommend AFRT as a validated treatment option for head and neck cancer patients."

Cediranib improves survival in recurrent ovarian cancer

WOMEN with ovarian cancer recurring after chemotherapy survive for longer after treatment with a new biological therapy.

Cediranib, taken in pill form and accompanying platinum-based chemotherapy, increased the time before the disease progressed from 9.4 months to 12.6 months over a period of 2 years, and increased overall survival time from 17.6 to 20.3 months.

An international randomised, double-blind, academic clinical Phase III trial, ICON6 enrolled a total of 456 women in 63 centres from the UK, Spain, Australia, and Canada. Patients were then randomised to receive the chemotherapy, accompanied with either a placebo - 20 mg daily of cediranib followed by placebo for 18 months, or cediranib which was prescribed at 20 mg a day during chemotherapy and used afterwards as a maintenance treatment.

"These are ground-breaking data," Prof Jonathon Ledermann, of University College London's Cancer Institute, said while presenting the results. "Cediranib is the first oral VEGF tyrosine kinase inhibitor that has been shown to delay tumour progression and improve overall survival in recurrent ovarian cancer. It is simple to give for a prolonged period, and in most patients it is well-tolerated."

Though adverse side-effects did include high blood pressure, diarrhoea, and fatigue, the ECCO's President, Prof Cornelis van de Velde also agreed that these results were important.

"Once the disease has recurred, there are few treatment options available that make a significant difference to its progression and to overall survival. The ICON6 trial shows that cediranib does make a difference, and it is to be hoped that it can be made available to women as soon as is practicable," he said.

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Lymph nodes treatment battles breast cancer

EARLY radiation therapy on lymph nodes behind the breast bone and above the collar bone increases the survival rate in breast cancer patients without increasing the added side-effects.

This new discovery was released at ECC 2013, where Dr Philip Poortmans, a radiation oncologist from the Institute Verbeeten, Tilburg, the Netherlands made various comments on these new findings.

This was an international randomised trial, involving 4,004 patients from 43 centres. Dr Poortmans stated: "Our results make it clear that irradiating these lymph nodes give a better outcome than giving radiation therapy to the breast/thoracic wall alone."

There are two pathways in which the cancer can disperse; the most prominent being the axilla (armpit), these lymph nodes can be treated by surgery and/or radiation therapy. The second drains to the internal mammary (IM) lymph nodes behind the breast bone, and also to the medial supraclavicular (MS) which are found above the collar bone. Many centres however, do not treat the IM-MS lymph nodes as there is little information available of the effects of treatment in these areas.

The results, after an average follow-up of 10.9 years, illustrated that patients in the IM-MS treatment group had a higher overall survival rate independent of the lymph nodes involved. There were also no serious complications relating to the treatment. The benefits of IM-MS radiation lie in the ability to eradicate microscopic tumour deposits in the lymph nodes.

Dr Poortmans added: "Interestingly, this effect is irrespective of the stage of the tumour. We believe that this is likely to be related to the positive interaction of the IM-MS treatment with systemic treatment – chemotherapy, hormonal therapy, and targeted treatment."

Where there is a lower risk of the cancer spreading outside of the breast, patients will be treated with a less invasive therapy to reduce the likelihood of side-effects, using IM-MS radiation. This locoregional treatment could also be used to eradicate disease in patients with a high risk of metastases.

> "Our results make it clear that irradiating these lymph nodes give a better outcome than giving radiation therapy to the breast/thoracic wall alone."
>
> *Dr Philip Poortmans, Institute Verbeeten, Tilburg, the Netherlands*

Everolimus: new hope for advanced papillary kidney cancer patients

The use of the anti-cancer drug everolimus for the treatment of advanced papillary kidney cancer has undergone Phase II studies.

Dr Bernard Escudier, Head of the French Group of Immunotherapy and Chairman of the Genitourinary Tumour Board at the Institut Gustave-Roussy in Villejuif, France, said: "Our results showed that for 59% of patients who received everolimus as their first-line treatment, their disease did not get worst and remained stable. These findings are important and indicate that more than half of these cancer patients are getting some kind of benefit from everolimus treatment."

Patients with papillary kidney cancer, the second most frequent type of kidney cancer which accounts for 15% of all kidney cancer cases, has a poor prognosis when metastasis occurs as there are no effective therapies.

Everolimus is an anti-cancer drug known as an mTOR (mammalian target of rapamycin) inhibitor, which is responsible for cell growth processes such as cell metabolism, growth, and proliferation. Failure to function correctly leads to cancer development.

Dr Escudier and colleagues recruited 92 patients into the RAPTOR (RAD001 in Advanced Papillary Tumour Program in Europe) study. The patients, who had never received systematic treatment, underwent the regime of taking the drug dosage of 10 mg once a day, for as long as they were tolerant to the medication.

Of the 92 enrolled patients, 83 were included in the intention-to-treat (ITT) analysis, and 63 were included in the per-protocol (PP) analysis. Tissue samples were analysed by pathologists, who examined the extent to which the cancer had spread.

In the PP analysis, the disease was stable in 59% of patients. Progression-free survival was 7.8 months (local investigators) and 3.9 months (independent investigators), and at least half of the patients were alive at 20 months. Similar results were seen in the ITT analysis.

Dr Escudier concluded: "While the results from this Phase II study are encouraging, a Phase III trial would need to be done to fully characterise the efficacy and safety profile of everolimus in this patient population."

EVIDENCE-BASED TREATMENT PLANNING IN mCRC: THE KEY TO MAXIMISING OUTCOMES

Summary of Presentations from the Roche Sponsored Satellite Symposium, European Cancer Congress 2013, Amsterdam, the Netherlands

Chairperson

Dirk Arnold[1]

Speakers

Eric Van Cutsem,[2] Sharlene Gill[3]

1. Medical Director of the Hubertus Wald Tumor Center at the University Cancer Center, Hamburg, Germany

2. Professor of Internal Medicine, Head of Digestive Oncology, University Hospital Gathuisberg, Leuven, Belgium

3. Associate Professor of Medical Oncology, British Columbia Cancer Agency, Vancouver, Canada

Disclosure: For speaker disclosures, see page 37.

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INTRODUCTION

This Roche sponsored satellite symposium was held as part of the European Cancer Congress 2013, and reviewed the current evidence available on treatment options for metastatic colorectal cancer and the application of this evidence to clinical practice.

Analysing the Current Treatment Landscape

Prof Eric Van Cutsem

Prof Van Cutsem began by presenting Phase III data from eight studies on first-line treatment regimens in metastatic colorectal cancer (mCRC), together with four observational studies. These studies compared overall survival (OS) and progression free survival (PFS) in patients treated with the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, in combination with oxaliplatin and irinotecan-based chemotherapy regimens as well as triplet chemotherapy regimens. They found a consistent survival benefit with addition of bevacizumab to the treatment regimens.[1-14] Mutations in the *KRAS* gene are present in 35–45% of colorectal cancers and result in activation of proliferation pathways.[15] The *KRAS* gene is a member of the *RAS* gene family.[15] Bevacizumab activity in combination with other therapeutics in *KRAS* wild-type mCRC patients, demonstrated consistently high OS and PFS.[2,3,16-18] The AVEX study analysed patients over 70 years of age treated with capecitabine chemotherapy, with or without bevacizumab, and also demonstrated PFS improvements in patients treated with bevacizumab, with a hazard ratio (HR) of 0.53.[19]

The use of epidermal growth factor receptor (EGFR) antibodies in first-line treatment was also discussed. Studies on *KRAS* wild-type patients treated with EGFR inhibitors in combination with irinotecan and oxaliplatin demonstrated benefit from addition of EGFR inhibitors to irinotecan-based regimens, but a mixed response in oxaliplatin-based regimens.[20-23] The PRIME analysis demonstrated a PFS and OS benefit in *RAS* wild-type patients treated with FOLFOX (combination therapy consisting of folinic acid,

fluorouracil and oxaliplatin) together with the EGFR inhibitor panitumumab. This finding was particularly noteworthy as the initial trial had not shown a survival benefit.[23] Prof Van Cutsem noted that this study looked at all *RAS* mutations and the data suggested that colorectal cancer patients should be tested for the spectrum of *RAS* mutations, rather than *KRAS* mutations alone.

Prof Van Cutsem then discussed maintenance therapy. In the Phase III CAIRO trial, patients received capecitabine, oxaliplatin and bevacizumab and were then randomised to observation or to receive maintenance therapy of bevacizumab plus capecitabine.[24] Bevacizumab and capecitabine were reintroduced after disease progression. There was a median progression from the moment of randomisation (PFS1) of 8.5 months for maintenance therapy versus 4.1 months for observation. The primary endpoint of the study was the time from randomisation to progression upon any treatment containing capecitabine and bevacizumab, given after PFS1 (TT2P). This also showed a benefit for maintenance with bevacizumab with a stratified HR of 0.67.

Two head-to-head trials of bevacizumab versus EGFR inhibitors in *KRAS* wild-type patients were presented. PEAK is a Phase II first-line study of untreated, unresectable, wild-type *KRAS* patients randomised to FOLFOX plus bevacizumab or FOLFOX plus panitumumab.[25] PFS was similar in both groups (10.1 and 10.9 in the bevacizumab and panitumumab group, respectively, p=0.22). The larger FIRE-3 Phase III study randomised almost 600 patients to receive FOLFIRI (combination therapy containing folinic acid, fluorouracil and irinotecan) plus bevacizumab or FOLFIRI plus EGFR inhibitor cetuximab; the cetuximab group showed an increase in OS but not PFS.[18] Prof Van Cutsem noted that while the outcome from this study was important, before changing clinical practice it would be necessary to wait for the results of the CALGB study of cetuximab, with or without bevacizumab, in combination with chemotherapy in *KRAS* wild-type mCRC patients.[26] This study is ongoing and may provide results next year. While traditionally *KRAS* testing has looked to identify mutations in exon 2, it has been shown that there is a lack of efficacy in patients receiving first-line panitumumab who have mutations in *KRAS*, *NRAS* and *BRAF* outside of *KRAS* exon 2.[23,25] Prof Van Cutsem considered this indicated a need to expand testing to a broader range of mutations in *KRAS* but also in *NFAS* and *BRAF*.

In second-line Phase III studies, only those using anti-VEGF agents, such as bevacizumab and aflibercept, showed significant survival difference when compared to chemotherapy alone.[27–29] Prof Van Cutsem raised the question: "Is there rationale to continue VEGF inhibition beyond disease progression?" The TML study demonstrated PFS benefit for continuing bevacizumab post progression (5.7 versus 4.1 months), while the smaller Bevacizumab Beyond Progression trial also showed PFS benefit, although this was non-significant.[28,30] The VELOUR trial studied second-line VEGF inhibitor aflibercept in patients and found a PFS benefit (6.7 versus 3.9 months).[29]

Lastly, Prof Van Cutsem discussed the use of biologicals in third or subsequent-line therapy. Data from the CO.17 study and Study408 demonstrated an increase in OS and PFS with addition of cetuximab and panitumumab, respectively, compared to best supportive care (BSC).[31,32] He also presented data from the CORRECT study that demonstrated both an OS (6.4 versus 4.0 months) and PFS (1.9 versus 1.7 months) benefit with addition of the broad spectrum kinase inhibitor, regorafenib, compared to BSC.[33] The relative benefit of EGFR inhibitors is larger in later-line therapy than it is in early-line treatment. Prof Van Cutsem noted that this is a consideration in treatment planning and highlighted a need for more strategic trials to explore this.[20,22,23,31,32,34–36] From the current available data, it is evident that bevacizumab is the only biological with OS benefits in first and second-line therapy.

Prof Van Cutsem concluded that the selection of EGFR inhibitors is important as these have the strongest survival benefit in later lines of therapy. A broader *RAS* mutation status may be more important than *KRAS* to identify patients that are not suitable for panitumumab, and potentially for cetuximab. One of the main challenges to address in the successful treatment of mCRC is the understanding of the disease biology. It was Prof Van Cutsem's opinion that different tools are needed in order to accomplish this.

Evidence-Based Treatment Planning in Real Life

Dr Sharlene Gill

Dr Gill's presentation focused on the translation of evidence on treatment for mCRC into practice. She explained that there are a number of Phase III trials of biologicals in mCRC that may help to define an optimal strategy. The challenge for treating mCRC patients is to determine whether upfront planning of their treatment ensures the best possible outcome.

Dr Gill presented the case of a 61-year-old man diagnosed in 2009 with stage III adenocarcinoma of the sigmoid colon. He wished to pursue intensive treatment and underwent primary resection of the T3N1 tumour plus two positive lymph nodes, followed by 12 cycles of adjuvant FOLFOX. This was well-tolerated, with the exception of some grade 1 reversible neuropathy. In 2011, he presented with metastatic disease to the liver. A subsequent positron emission tomography scan confirmed para-aortic and portal adenopathy and, on this basis, it was deemed unresectable. He had wild-type *KRAS*. His Eastern Cooperative Oncology Group (ECOG) status (a scale to measure a patient's performance) was 0 (fully active, able to carry on all pre-disease performance without restriction) and he had elevation of tumour marker carcinoembryonic antigen (CEA) at 266 ng/mL with relatively few comorbidities; he had well-controlled hypertension and gastro-oesophageal reflux disease (GERD) with no history of cardiovascular disease or thrombotic events.

Dr Gill considered the evidence for first-line therapy if OS were the primary goal of treatment. Bevacizumab has shown survival benefit, irrespective of *KRAS* mutation status, and cetuximab has shown an OS benefit in *KRAS* wild-type patients; either choice would be reasonable for treatment of the patient.[6,16,20,23] However, Dr Gill also discussed the need to consider the continuum of care when choosing first-line treatment. The ESMO guidelines from 2012 recommend chemotherapy plus bevacizumab in first-line therapy, and at first progression, chemotherapy plus bevacizumab in second-line therapy.[37] Later lines of therapy can be dictated by *RAS* mutation status – wild-type *KRAS* patients could be offered EGFR inhibitor therapy at third-line followed by regorafenib at progression, or mutated *KRAS* patients could be offered regorafenib at third-line.[31,33]

As a result of the recommendations in the guidelines, the patient received FOLFIRI plus bevacizumab for 13 months, which was tolerated well. After some initial grade 1 diarrhoea, he had a partial response. He progressed at 13 months but maintained an ECOG score of 0. While moving to second-line therapy, Dr Gill questioned which biological agents were best at providing an OS benefit. While EGFR inhibitors have demonstrated response rate and progression-free survival activity, no statistical difference in overall survival is seen with their use in second-line treatment.[35,38] There is evidence that bevacizumab use beyond first-line progression improves survival.[27,28] Aflibercept data from the VELOUR study in second-line therapy had also shown improved survival.[29] In comparing the data on second-line aflibercept to that on second-line bevacizumab, similar differences in OS for the two regimens were identified and Dr Gill postulated that, in the absence of a head-to-head comparison, the efficacies of both seem comparable.[27-29] Considering this, she noted that toxicities were now a valid issue and that aflibercept is associated with increased chemotherapy-associated and anti-VEGF toxicity.[27-29] Therefore if a patient was tolerating bevacizumab well, there would be little rationale for moving to aflibercept. Her patient remained on bevacizumab and switched to FOLFOX from FOLFIRI, after which he experienced grade 2 neuropathy and was switched to bevacizumab plus capecitabine. His disease remained stable for 8 months and then progressed with an ECOG of 1 (some restrictions in activity).

Dr Gill discussed potential third-line therapies. She considered that EGFR inhibitors display better efficacy in later lines of therapy and that regorafenib in wild-type *KRAS* patients could be an option after EGFR inhibitor treatment and in subsequent lines of therapy.[31,33,39] Her patient was given irinotecan plus cetuximab and displayed partial response, but had significant toxicity with grade 2 diarrhoea, a rash, and a PFS of 5 months. He was then treated with fourth-line therapy regorafenib, but progressed after 2 months with toxicity. In total, the patient had approximately 26 months PFS on treatment and was entered onto a clinical trial where expected OS from time of diagnosis was approximately 30 months.

Dr Gill considered alternative scenarios for her patient. He could have received bevacizumab plus FOLFOX rather than FOLFIRI in first-line therapy.[1,2] Dr Gill noted that this would be a reasonable choice; however, FOLFOX is associated with toxicity and cumulative neurotoxicity should be considered if treating until progression. Bevacizumab plus FOLFOX followed by maintenance bevacizumab plus capecitabine could also be considered. Second-line therapy could be bevacizumab plus FOLFIRI.[28] Third-line therapy could be EGFR inhibition with cetuximab or panitumumab, and if the patient was well he could be offered regorafenib when other options were exhausted.[31–33]

Another alternative considered was triplet therapy FOLFOXIRI (a combination of folinic acid, fluorouracil, oxaliplatin, and irinotecan) plus bevacizumab in first-line, since patients treated with this combination have increased PFS compared to those treated with FOXFOX plus bevacizumab.[10] However, this regimen was associated with increased toxicity, resulting in diarrhoea, neutropaenia, and stomatitis and increased risk of neurotoxicity. The choice of second-line therapy would depend on the reason for switching; if the reason for switching was disease progression, then the likely option would be EGFR inhibitors, possibly with irinotecan followed by third-line regorafenib;[34-36] however, if switching was due to toxicity, it would be FOLFIRI plus bevacizumab and an EGFR inhibitor in third-line, regorafenib in fourth-line.[28,31–33] Thus, Dr Gill noted that upfront triplet therapy could reduce the number of subsequent lines of therapy available, but the data indicated that this would not impact survival.

Dr Gill concluded that in order to achieve the best outcome for mCRC patients, it is important to look at the best available evidence and define an upfront treatment strategy. There is strong Phase III data to support the efficacy of bevacizumab and, when used in first-line therapy, allows VEGF suppression in second-line therapy. It also saves EGFR inhibitor use for subsequent lines of therapy and is useful irrespective of *KRAS* status.

Panel Discussion

A panel discussion followed the presentations, which focused on the considerations given to treatment in the clinic and the discussion of treatment strategy with patients. Prof Van Cutsem felt that the use of an optimal strategy sequence was the best way to optimise patient survival; however, Dr Gill's opinion was that, while the entire sequence would need to be considered upfront, all potential lines of therapy would not necessarily be discussed with patients at the time of initiating treatment, partly because particular treatment options change over time. Moreover, while patients need to know that further therapeutic options are available, the specific details regarding later lines of therapy may be overwhelming. Chairperson Prof Arnold questioned how to change strategy after a treatment was stopped due to toxicity issues. Dr Gill noted that this is a challenge, but her preference was to maximise survival without exposing the patients to too much toxicity, and she would rarely use triplet therapy for unresectable mCRC. Finally, Prof Van Cutsem emphasised the need to expand the testing of *KRAS* to *RAS*, although this would not necessarily change first-line strategy, and noted that the upcoming CALGB study data would prove useful in this regard.

REFERENCES

1. Saltz LB et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013–9.

2. Tol J et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563–72.

3. Hecht JR et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27:672–80.

4. Diaz-Rubio E et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Oncologist. 2012;17:15–25.

5. Schmoll HJ et al. Cediranib with mFOLFOX6 versus bevacizumab with mFOLFOX6 as first-line treatment for patients with advanced colorectal cancer: a double-blind, randomized phase

III study (HORIZON III). J Clin Oncol. 2012;30:3588–95.

6. Hurwitz H et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.

7. Sobrero A et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology. 2009;77:113–19.

8. Fuchs CS et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. J Clin Oncol. 2008;26:689–90.

9. Fuchs CS et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol. 2007;25:4779–86.

10. Falcone A et al. FOLFOXIRI/bevacizuman (bev) versus FOLFIR/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. Abstract 3505, presented at ASCO 31 May–4 June 2013, Illinois, USA.

11. Arnold D et al. First-line treatment with bevacizumab plus chemotherapy for patients with metastatic colorectal cancer: Results from a large German community-based observational cohort study. Poster discussion PD-0006, presented at WCGC 30 June–3 July 2010, Barcelona, Spain.

12. Kozloff M et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist. 2009:14:862–70.

13. Van Cutsem E et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol. 2009;20:1842–7.

14. Bendell JC et al. Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: results from ARIES, a bevacizumab observational cohort study. Oncologist. 2012;17:1486–95.

15. Tan C, Du X. KRAS mutation testing in metastatic colorectal cancer. World J Gastroenterol. 2012;18:5171–80.

16. Hurwitz HI et al. The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer. Oncologist. 2009;14:22–8.

17. Price TJ et al. Impact of KRAS and BRAF gene mutation status on outcomes from the Phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer.J Clin Oncol. 2011;29:2675–82.

18. Heinemann V et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). Abstract LBA3506, presented at ASCO 31 May–4 June 2013, Illinois, USA.

19. Cunningham D et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol. 2013;14:1077–85.

20. Van Cutsem E et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29:2011–9.

21. Tveit KM et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol. 2012;30:1755–62.

22. Maughan TS et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet. 2011;377:2103–14.

23. Douillard JY et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369:1023–34.

24. Koopman M et al. Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG) Abstract 3502, presented at ASCO 31 May–4 June 2013, Illinois, USA.

25. Schwartzberg LS et al. Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC). ASCO 31 May–4 June 2013, Chicago, Illinois. Abstract 3631, presented at ASCO 31 May–4 June 2013, Illinois, USA.

26. Venook AP. Abstract discussion: Subsets of patients with colorectal cancer – who benefits and who does not? Presented at the 15th WCGC 6 July 2013, Barcelona, Spain.

27. Giantonio BJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25:1539–44.

28. Bennouna J et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013;14:29–37.

29. Van Cutsem E et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30:3499–506.

30. Salvatore L et al. Bevacizumab beyond progression in metastatic colorectal cancer patients receiving a first-line treatment containing bevacizumab: Update of BEBYP trial by GONO. Abstract number O-0027. Presented at the 15th WCGC 6 July 2013, Barcelona, Spain.

31. Karapetis CS et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359:1757–65.

32. Amado RG et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26:1626–34.

33. Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:303–12.

34. Seymour MT et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol. 2013;14:749–59.

35. Langer C et al. Mutations in patients with metastatic colorectal cancer receiving cetuximab in combination with irinotecan: results from the EPIC trial. ESMO 2008, Abstract 385P. Ann Oncol. 2008;19(8):viii133.

36. Peeters M et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28:4706–13.

37. Schmoll HJ et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol. 2012;23:2479–516.

38. Sobrero AF. Final results from study 181: Randomized phase III study of FOLFIRI with or without panitumumab (pmab) for the treatment of second-line metastatic colorectal cancer (mCRC). Abstract number 387. Oral abstract session, presented at ASCO 19 January 2012, San Francisco, California.

39. Jonker DJ et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357:2040–8.

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THE FUTURE OF CHRONIC LYMPHOCYTIC LEUKAEMIA TREATMENT: BALANCING EFFICACY, SAFETY AND COST

A Review of the Mundipharma International Ltd Organised Symposium, at the International Workshop on Chronic Lymphocytic Leukemia (iwCLL), Cologne, Germany, 9th-11th September 2013

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Expanding Treatment Options for Less Fit CLL Patients

Dr Valentin Goede

So far, there is no objective and broadly accepted definition of the less fit chronic lymphocytic leukaemia (CLL) patient. There is great heterogeneity in fitness among elderly patients. This means that patient populations should be checked in clinical trials that claim to provide data for less fit CLL patients.

One treatment option for less fit CLL patients is chemotherapy alone; the question is which chemotherapy is the best treatment choice. There are several Phase II trials evaluating the efficacy and toxicity of fludarabine-based chemotherapy in older or unfit patients,[1-4] the results of the trials varied, the patient numbers were rather low and patient populations were heterogeneous. Therefore, it is not possible to conclude from these trials whether fludarabine treatment is more or less suitable in less fit CLL patients. The German CLL study group (GCLLSG) initiated a Phase III trial with fludarabine monotherapy[5] in elderly patients. The results showed that there was no difference in progression-free survival (PFS) between fludarabine and chlorambucil (19 months versus 18 months respectively, p=0.7). Furthermore, fludarabine did not increase overall survival (OS) (46 months in the fludarabine versus 64 months in the chlorambucil arm, p=0.15).

During recent years chemoimmunotherapy has been very successfully developed in younger, fit patients, the question is whether it can be used in unfit patients. There are ongoing Phase II trials with low-dose fludarbine-based chemoimmunotherapy (fludarabine plus cyclophosphamide plus rituximab [FCR]) in elderly and possibly less fit CLL patients.[6-8] The studies include a larger patient population and the initial data are promising, but there are no Phase III data available comparing FCR low dose regimen with any other treatments in this particular patient population.

Bendamustine is another chemotherapy option for the treatment of CLL but there are no Phase II trials specifically conducted for elderly and less fit CLL patients. However, there are promising retrospective data available[9] that show first-line treatment with bendamustine in patients with a median age of 72 years (n=10); the overall remission rate (ORR) was 10%, the complete response rate (CR) 10% and median PFS was 26 months. A larger Phase III trial[10] compared first-line bendamustine monotherapy with chlorambucil

monotherapy. The results showed that there was no OS advantage with bendamustine compared to chlorambucil, but there was a clear advantage regarding PFS (median PFS was 21.6 months with bendamustine and 8.3 months with chlorambucil, p<0.0001). Unfortunately, the median age of the patient population was 65 years which makes it difficult to draw definitive conclusions across all patient populations.

Bendamustine-based chemoimmunotherapy (bendamustine plus rituximab [BR])[11-13] is a further treatment option. Data produced by the GCLLSG[11-13] show encouraging results, particularly in one trial[11] that showed first-line treatment with BR had a promising efficacy profile and PFS of 34 months, although the median age was only 64 years. Retrospective data of BR in elderly patients[9] (median age 73 years; n=6) show encouraging response rates in first-line treatment. The overall response (OR) was 67%, CR 33% and partial response (PR) 33%. There are no Phase III data available at present for BR treatment in less fit patients. However, there is one study that is in progress,[14] the MaBLe study, which is comparing bendamustine plus rituximab with chlorambucil plus rituximab. The median age of the trial population was 75 years in the bendamustine plus rituximab arm (n=58) and 73 years in the chlorambucil plus rituximab arm (n=73). There were no data available regarding the fitness of patients but many of the patients had concomitant medications indicating the likelihood of comorbidities. The preliminary results of the study show that there was no significant difference in OR between the two treatment arms. However, there was an increased CR rate in the bendamustine plus rituximab arm. The preliminary data showed that the toxicities for both treatments were similar, suggesting that bendamustine plus rituximab was not significantly more toxic than chlorambucil plus rituximab.

Chlorambucil-based chemoimmunotherapy (chlorambucil plus rituximab [CLB-R]) is another treatment option in less fit CLL patients. Phase II trials with CLB-R in elderly patients[15,16] show promising response rates which are higher than would be expected with chlorambucil monotherapy and in one study the median PFS was 24 months.[15] A Phase III study[17] compared chlorambucil plus rituximab with chlorambucil monotherapy. The response rates and PFS were higher in patients treated with CLB-R than with chlorambucil monotherapy, this was particularly seen in unfit patients.

There are novel CLL drugs likely to be available in the near future which will further complicate treatment choice. These include lenalidomide which was pioneered in a Phase II trial in elderly patients and has been compared with chlorambucil in a Phase III trial, unfortunately the Phase III study has been stopped because of a high mortality rate in the experimental arm. ABT199 is also being studied but not specifically in unfit CLL patients. In addition, two novel CD20 antibodies (obinutuzumab and ofatumumab) are being developed. The CLL11 trial[18] is comparing GA101 plus chlorambucil (G-CLB) with chlorambucil (CLB) alone in CLL patients who are unfit and have comorbidities. The trial is showing promising response rates.[17]

Preliminary results for the OR and CR for G-CLB were better compared with the CLB arm. The median PFS showed superior efficacy with G-CLB compared to CLB alone. There are both monotherapy and combination data available on tyrosine-kinase inhibitors (TKIs), specifically in the first-line treatment of elderly patients. Ibrutinib monotherapy has been evaluated in 31 patients with a median age of approximately 70 years; preliminary results show an excellent PFS. Similarly, in elderly patients receiving a combination of idelalisib plus rituximab the PFS was very promising.[19,20]

Treatment is moving in the direction of considering the less fit patients rather than a homogenous population. It is possible that there are patients who are not completely fit but are fit enough to be treated with chemoimmunotherapy. Regimens used outside clinical trials indicate that there are a proportion of less fit patients that are good candidates for treatment with either BR or CLB-R chemoimmunotherapy. There are patients that are almost too frail to treat; for these patients there appears to be a niche for monochemotherapy, and bendamustine may be a treatment option. Rituximab and ofatumumab monotherapy are used in the USA for the treatment of this group of patients. However, there is sparse trial evidence available to support their use. The novel treatments have the potential to be used in less fit patients. The patients that would normally be treated outside of clinical trials with chemoimmunotherapy are good candidates

to be treated with chemoimmunotherapy with one of the new CD20 antibodies. Chemoimmunotherapy-free treatment can also be considered by combining novel CD20 antibodies or rituximab with a TKI. Patients who are almost frail and would usually be treated chlorambucil or bendamustine monotherapy are good candidates to be investigated for treatment with the novel drugs as a monotherapy, e.g. TKIs or possibly CD20 antibodies. This would provide additional data on the use of the novel agents and their use in less fit patients.

'Go-Go' (Patients in Good Physical Condition) CLL Patients: A Look Towards the Future

Prof Clemens Wendtner

Between 2005 and 2006 the gold standard was set by the MD Anderson Cancer Center with the fludarabine plus cyclophosphamide plus rituximab (FCR) regimen for the treatment of CLL. In addition, the GCLLSG has conducted a Phase III trial comparing fludarabine plus cyclophosphamide (FC), the old standard of care, versus FCR.[21] The results show that FCR produces a remarkable median PFS of almost 5 years and a benefit in OS in first-line CLL treatment.

FCR is the gold standard first-line treatment for go-go patients. Following a median observation time of 5.9 years the data have been updated[22] (Figure 1) and show that there is a clear difference in PFS between FCR and FC treatment. Median PFS for FCR is 57 months compared with 33 months for FC (HR 0.59; 95% CI 0.5-0.7; p<0.0001).

In addition, OS showed increased benefit for the FCR treated patients (69.4% alive, median not reached) compared with the FC treated patients (62.3% alive, median 86 months. HR 0.68; 95% CI 0.535-0.858; p=0.001); these results show that FCR is a proven standard of care for CLL patients. Böttcher et al.[23] showed that PFS and OS can be predicted by collecting peripheral blood at different time points (interim staging and first restaging) after treatment with FCR. PFS showed that irrespective of treatment the probability of negative minimum residual disease was higher using FCR than FC. This was also shown in OS.

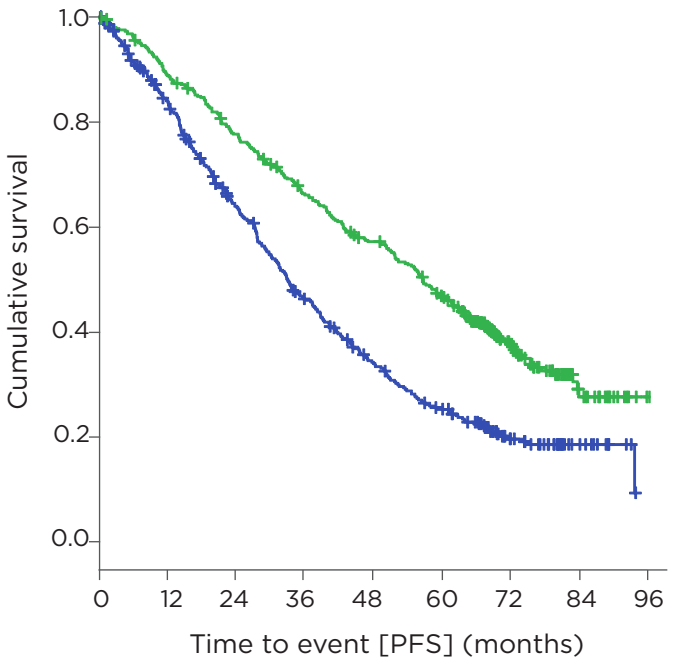

Figure 1. Addition of rituximab to fludarabine and cyclophosphamide: progression-free survival 2012. FCR: fludarabine plus cyclophosphamide plus rituximab; FC: fludarabine plus cyclophosphamide. Median observation time: 5.9 years. Median progression-free survival: FCR: 57 months, FC: 33 months. HR 0.59, 95% CI 0.5-0.7, p<0.0001. *Fischer K et al.*[22]

In go-go patients, good results have been achieved in PFS and OS using FCR but there are a fraction of patients that do not benefit in the long-term. One notion is that additional treatment is required following induction therapy in the maintenance period, e.g. lenalidomide. Consequently the CLLM1 study was established.[24] This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study of the efficacy and safety of lenalidomide as maintenance therapy for high-risk patients with CLL following first-line therapy. The trial is ongoing and will provide information on the role of lenalidomide in the maintenance setting.

FCR therapy induces significant toxicity, predominantly neutropenia and infections, between one-fifth and one-quarter of patients treated with FCR will develop severe infections (Grade 3 or 4).[21] The issue of neutropenia is frequently being discussed; FCR induces more severe neutropenia at the beginning of treatment compared to FC. However, in the long-term this

Table 1. Addition of rituximab to fludarabine and cycleophosphamide: toxicities after the end of treatment (N=800).

Late neutropenias 2 months after end of treatment	N	%	p value
FCR	67	16.6	0.007
FC	35	8.8	
Late neutropenias 12 months after end of treatment	**N**	**%**	**p value**
FCR	16	3.9	0.7
FC	15	3.7	

Fischer K et al.[22]

toxicity appears to be neutralised[22] (Table 1). In addition, secondary malignancies following intensive chemotherapy (including FCR) occur. The CLL8 trial[22] showed that 13.1% of patients had secondary malignancies in the FCR arm compared with 17.4% in the FC arm (median time to onset 21.5 months [range 0-80], p=0.095). In future treatment concepts the issues that arise from chemotherapy should to be considered and if possible avoided.

In addition to FCR, the use of BR has been investigated in go-go patients in a Phase II trial.[11] The results of the trial showed an OR rate of 88.0% (95% CI 80.7-100.0%) with a CR rate of 23.1% and a PR rate of 64.9%. The side-effects that occurred were Grade 3 or 4 severe infections in 7.7% of patients and Grade 3 or 4 adverse events for neutropenia, thrombocytopenia and anaemia were documented in 19.7%, 22.2% and 19.7% of patients, respectively. These results indicate that there are fewer side-effects with BR than FCR, particularly the number of severe infections recorded. Nevertheless, it remains open to debate which therapy is more efficacious.

An analysis of the historic data of the results in Phase II trials[11,21] using FCR, FC or BR shows that PFS in patients treated with FCR was 77.6% versus 71.9% with BR and 63.9% with FC. In terms of OS there was negligible difference between the therapies (Table 2).

Table 2. Side-by-side analysis of progression-free survival and overall survival rates with fludarabine plus cyclophosphamide plus rituximab, fludarabine plus cyclophosphamide, and bendamustine plus rituximab.

Progression-free survival				
PFS	**pts, N**		**Median, months**	**24-months survival, %**
All patients	934	610 (65.3)	41.8	71.0
First-line treatment				
[1]CLL8	817	550 (67.3)	42.5	70.9
FCR	408	253 (62.0)	56.8	77.6
FC	409	297 (72.6)	32.9	63.9
[2]CLL2M BR	117	60 (51.3)	37.5	71.9
Overall survival				
OS	**pts, N**		**Median, months**	**24-months survival, %**
All patients	934	298 (31.9)	89.2	89.7
First-line treatment				
[1]CLL8	817	279 (34.1)	90.2	89.7
FCR	408	154 (37.7)	85.8	88.0
FC	409	125 (30.6)	NR*	91.3
[2]CLL2M BR	117	19 (16.2)	54.8	90.2

△5.7%

△1.1%

* Not reached

FCR: fludarabine plus cyclophosphamide plus rituximab; FC: fludarabine plus cyclophosphamide; BR: bendamustine plus rituximab; PFS: progression-free survival; OS: overall survival.

Hallek MH et al.[21]

Fischer K et al.[11]

A Phase III trial, CLL10 study, of the GCLLSG[25] evaluating first-line therapy of fludarabine, cyclophosphamide and rituximab in physically fit CLL patients without deletions of the short arm of chromosome 17 (del 17p) has achieved the core goal and the study has been closed. The data have been submitted to the American Society of Hematology (ASH) and it is hoped that the results of the trial will provide guidance on the best treatment for go-go patients in the future.

In the meantime, alternative therapy management is being considered, for example it may be possible to build on BR therapy for go-go patients. Consequently, the CLL2P trial[26] was initiated using lenalidomide in addition to BR but it was found that in this trial the combination was not feasible so the trial has been closed. Another suggestion is that the CD20 antibody is exchanged; the GCLLSG is planning the CLLR3 trial in which GA101 is used for maintenance. The patients will be randomised to one of two arms: fludarabine plus cyclophosphamide plus GA101 or bendamustine plus GA101. This trial will allow exploration of the use of the new CD20 in maintenance therapy. Furthermore, there are other new agents that are becoming available that inhibit the B cell receptor pathway, these new agents inhibit specific targets; fostamatinib targets spleen tyrosine kinase (SYK), PCI 32765 targets Bruton's agammaglobulinemia tyrosine kinase (BTK) and CAL-101 (GS-1101) targets phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit *delta* (PI3Kδ). Byrd et al.[27] assessed the safety and efficacy of ibrutinib, a BTK inhibitor, in patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL). The results showed that these high-risk patients with 17p or 11q deletion do not do as well in terms of PFS and OS compared with patients who have no 17p or 11q deletion. One way to intensify these small molecules for high risk and go-go patients is to add a CD20 agent. Burger et al.[28] found that the BTK inhibitor ibrutinib in combination with rituximab (iR) is well tolerated and displays profound activity in high-risk CLL patients. Initial data show that time to treatment failure of iR treated 17p deleted patients is improved compared with patients treated with chemoimmunotherapy alone. These results are from a short follow-up period and long-term data are required. The Helios trial[29] is an ongoing Phase III trial in physically fit patients with relapsed or refractory CLL or SLL evaluating BR plus ibrutinib versus BR plus placebo. It is expected that the results of this study will indicate whether the addition of a small molecule in the induction phase is of value for patients. However, the problem of resistance[30] has to be addressed. It is known from other TKIs used to treat chronic myeloid leukaemia that there are resistance problems; hence in the future the emergence of second and third generation TKIs for CLL may be seen.

Another approach to treatment of patients with CLL is to interfere with the apoptotic pathway. There are a group of drugs that target the B cell CLL/lymphoma 2 (BCL2) and are thus able to regulate apoptosis through the mitochondria; using ABT-199, a BCL-2 inhibitor, induces Bax/Bak activation by BH3 and stimulates the release of cytochrome-C to induce cell death. The use of ABT-199 has been trialled in a Phase I first-in-human study in patients with relapsed or refractory CLL.[31] The results showed a dramatic response in nodal size reduction in the majority of patients (n=51), median time to 50% reduction was 1.4 months (range 0.7-13.7) in a very short time period.

The future concepts of the GCLLSG include a number of Phase II trials for all-comers; these include go-go patients and unfit patients. The trials will use different combinations of drugs with an initial round of chemotherapy, and the GA101 antibody as maintenance, the proposed trials are:

- CLL2-BIG: Bendamustine followed by GA101 and ibrutinib; followed by ibrutinib and GA101 maintenance.
- CLL2-BAG: Bendamustine followed by GA101 and ABT-199; followed by ABT-199 and GA101 maintenance.
- CLL2-BCG: Bendamustine followed by GA101 and CAL-101; followed by CAL-101 and GA101 maintenance.

In addition, specific large Phase III trials are planned; the CLL13 trial is for go-go patients and is based on the CLL10 trial using BR and/or FCR. CLL13 will assess BR/FCR versus BR/FCR plus CC-292 (a BTK inhibitor) in patients with previously untreated CLL. The CLL14 trial will involve GA101 and ABT-199 followed by ABT-199 maintenance versus six cycles of GA101 + CLB in CLL patients with comorbidities.

The Economic Burden of CLL Treatment Now and in the Future

Dr George Follows

There are different views on how healthcare can be provided. In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) guidance supports healthcare professionals and others to make sure that the care they provide is of the best possible quality and offers the best value for money. In the USA there is a lot of debate about the Patient Protection Act and the Affordable Care Act; one view is *"The new health reform law -- the so-called Patient Protection and Affordable Care Act -- creates 159 new boards, commissions and agencies that will destroy the doctor-patient relationship and replace it with federal bureaucrats deciding who gets care and what treatments they can receive"* (Jason Millman). Politicians get very nervous about news headlines especially those which highlight the use of therapies in Europe that are not permitted in the UK, e.g. *'Betrayal of 20,000 cancer patients: Rationing body rejects ten drugs (allowed in Europe) that could extend lives'.*[32]

The UK works within a framework for calculating cost-effectiveness (NICE/Scottish Medicines Consortium [SMC]). The cost-effectiveness analysis is summarised using the expected incremental cost-effectiveness ratio (ICER);[33,34] this calculates the amount you have to spend to deliver a change in quality: ICER = change in costs/change in effectiveness. Change in effectiveness or clinical outcome is described using quality-adjusted life years (QALY);[33,34] the ICER is the cost of the treatment divided by QALY, this results in the extra years of life of given quality a person might gain as a result of treatment.[35] A very simplified example could be the following; a 60-year-old patient with acute myeloid leukaemia who would die without treatment has £100,000 spent to cure him and he lives 10 healthy years. Therefore, the patient's individual ICER is 10,000. However, if five patients are treated and only one survives then the overall ICER for the therapeutic intervention is 50,000. There is no doubt that society has to decide what it is willing to pay per QALY[33] and there will be a division (Figure 2)[36] in terms of balancing cost effectiveness and efficacy.

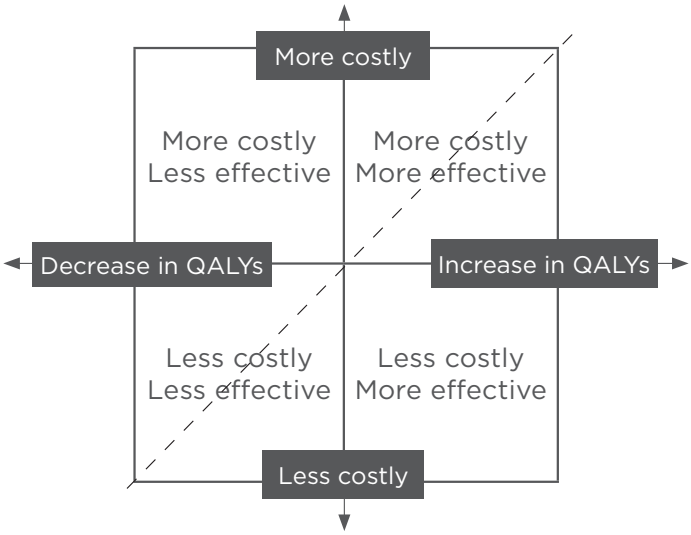

Figure 2. How do we decide on cost-effectiveness, i.e. society's willingness to pay for the quality-adjusted life year?
QALY; quality-adjusted life year.
NICE briefing paper.[33]
Image adapted from Laupacis A et al. [36]

The society's healthcare model will have to decide where it draws the line.

In the UK, the cost-effectiveness threshold of NICE/SMC indicates approximately £30,000 per QALY gained. There is continued debate about rarer conditions and orphan drugs; the EU legal definition of an orphan drug is the drugs used to treat a disease with the prevalence of <5 per 10,000 population. It is appreciated that drugs with orphan drug status increase the ICER, often the situation occurs where there is an ICER of >£30,000/QALY, but the treatment may still be defined as cost-effective, e.g. imatinib for the treatment of blast crisis chronic myeloid leukaemia with an ICER of £48,000, is the highest ICER for a treatment that has been approved in the UK. Special considerations are therefore given by the UK authorities where appropriate, e.g. the management of previously untreated conditions and 'ultra-orphan' drugs[37] (for conditions with a UK prevalence of <1 in 50,000).[38] This allows for greater expenditure to treat patients with 'ultra-orphan' drugs; for example for the treatment of Gaucher's disease (types I and III) with imiglucerase (Ceredase) has a preliminary estimated ICER of £391,244 per QALY in 270 patients in the UK.

Table 3. The present drug costs for chronic lymphocytic leukaemia regimens.

Regimen	Cycles of treatment	Line of treatment	Drug cost
Chlorambucil[i]	4.9	1st	£92
Bendamustine[i]	4.9	1st	£4,741
Fludarabine[ii]	6	1st	£2,812
Rituximab–fludarabine, cylophosphamide[ii]	6	1st	£12,940
Ofatumumab[iii]	12	Double refractory	£40,856*
Chlorambucil–rituximab[iv,v]	6	1st	£9,333
Bendamustine–rituximab[iv,v]	6	1st	£14,057

*Without patient access scheme

There are hugely difficult areas within pharmacoeconomics which include calculating the true cost of a regimen and what the true QALY gain for an intervention is; this can only be taken from trial data (PFS versus OS etc.) and trial patients do not necessarily represent the 'real world'.

The UK costs for CLL regimens (Table 3) range from chlorambucil which costs very little (£92) to current regimens with rituximab-fludarabine, cyclophosphamide (£12,940) or bendamustine–rituximab (£14,057).

It is not just the cost of the drugs that needs to be considered, there are additional aspects of care which include day unit time, supportive care drugs, short-term toxicities, additional investigations and longer-term toxicities. However, longer remissions equate to a better state of health, which potentially means fewer additional rounds of chemotherapy and improved QoL in remission which could potentially correlate with reduced broader healthcare costs. However, the standard of care, as defined by clinical trials does not mean this standard of care is applicable to all. A good example is FCR which is an international standard of care for CLL, but the patients recruited to the large randomised German CLL8 trial had a median age of 61 and an excellent performance status. We know from other large databases, such as the North of England Haematological Malignancy Research Network, that only a small percentage of patients are recruited into trials, and the age distribution of trial patients does not reflect the true age distribution of all patients. This highlights further that trial populations are often not representative of the 'real world'. This is the problem in clinical practice; if a pharmacoeconomic perspective is used and the ICER benefit is calculated for the use of FCR, this calculation is applicable to a 61-year-old with a median cumulative illness rating scale (CIRS) score of 0 or 1. Goede et al.[39] showed in the CLL8 trial that as comorbidities are accumulated the OS is reduced, raising the question of confidence in incremental cost-effectiveness ratio if the patient is unfit. The difficulty is that doctors are not actuaries, the aim is not to plan out the life expectancy of patients, but it does raise the question of survival. Across UK CLL trials (before the rituximab era) approximately one-third of patients had died within 4 years of starting first-line therapy. Of that third it is not known how many had died because of CLL and how many died because of their natural life expectancy. Should a patient's natural life expectancy influence decisions with regards to therapy? This is dangerous territory because in clinical practice if a patient, in actuarial terms, has a short life expectancy a cost economist would question the correctness of spending large amounts of money on cancer drugs. In practice this is the precarious domain of confusing age and comorbidity. As age increases people become survivors e.g. a woman in the UK who is 80 years old has a median survival of 9.1 years.[40] This would mean she would potentially have many years to benefit from novel therapies and if the person is fit it is likely that the median survival at 80 is more than 9.1 years.

The correlation that comorbidities will shorten life expectancy is not as straightforward as it appears. The Mayo clinic[41] evaluated their presenting CLL patients and found that the patients had a median of two comorbidities and half of them had a serious comorbidity. The assumption that the patients with a serious comorbidity would not survive as long as those without a serious comorbidity was difficult to prove within the data set. However, the data did show that if a patient was ineligible for a clinical trial, another marker of fitness, then there was a reduced survival rate. German data[42] from the CLL4 and

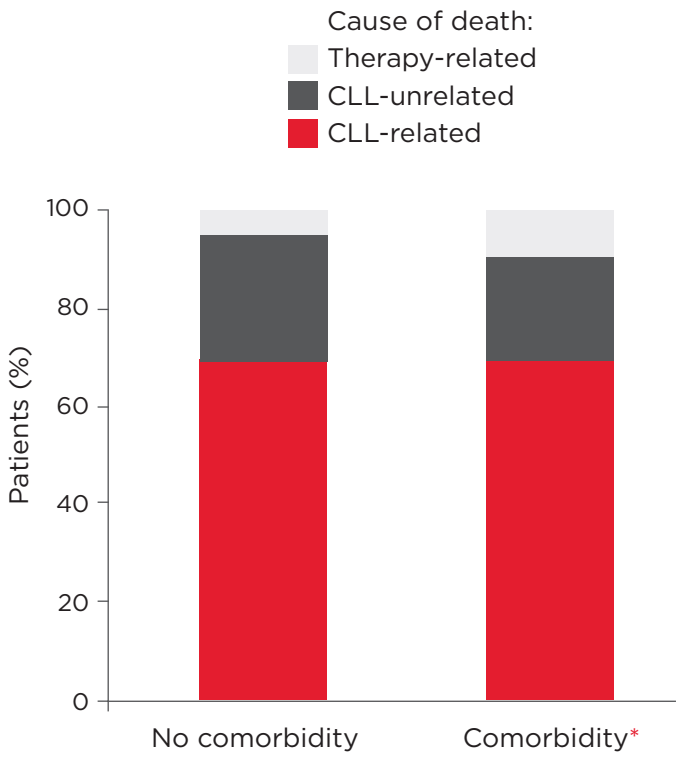

Figure 3. Comorbidities and life expectancy as presented by data from CLL4 and CLL5 trials. *Commonly Hypertension, Diabetes, Coronary Heart Disease.
Cramer P et al.[42]

CLL5 trials showed that at entry to the trials comorbidity was present in 53% of the patients and 25% had at least two comorbidities. PFS and OS were significantly shorter in comorbid patients (median OS 43.5 months versus 51.6 months; p=0.01; PFS was 20.3 months versus 23.5 months; p=0.03). The cause of death in these patients was analysed and the results showed that CLL-unrelated death which hypothetically should be higher in patients with comorbidities (commonly hypertension, diabetes and coronary heart disease) was actually similar to patients with no comorbidity (Figure 3).

A new era is on the horizon and consequently these are tremendously exciting times. However, this is causing huge disquiet, for example recently the UK press reported that: 'Of the 12 drugs approved by the Food and Drug Administration in the US in 2012, 11 were priced above $100,000 (£65,000) per patient per year. In addition the price of existing drugs of proven effectiveness has been increased by up to threefold.'[43] The cost of the novel agents to treat CLL is unknown as a monotherapy and novel agents used as a combination therapy will increase costs considerably.

In 2008 there were 2,798 patients diagnosed with CLL in the UK;[44] if a median 10-year life expectancy is assumed there are around 30,000 patients with CLL in the UK at any one time. If CLL management costs increase to £100,000 per patient per year when a patient is being treated with one or a combination of novel therapies, this will have a significant impact on funding. Assuming 50% of the patients will require treatment at some point, and 50% of the patients will be on therapy for 50% of their treatment lifetime, an approximate calculation would equate to £0.75 billion per year for the treatment of CLL. In addition there are ongoing costs; the current median survival for CLL patients is around 10 years. As survival increases with newer therapies, costs have the potential to increase disproportionately, as these patients will be surviving their CLL, and will begin to incur additional healthcare expenses of older age. The total NHS healthcare budget for England is £95.6 billion for 2013/2014; clearly the NHS cannot spend 0.5% of its budget on a single disease! This indicates that rationing will have to be implemented because there are inevitable cost limitations that will inhibit free access to these drugs in the UK healthcare environment.

There are issues that need to be addressed to enable the use of novel agents in the treatment of CLL. The science needs to be driven so that patient groups that will benefit most from the drug can be identified (e.g. will certain genomic subgroups of CLL benefit disproportionately from specific novel therapies). Clinical trials should be pushed to ascertain whether these novel agents can be used in a more intelligent way, to move away from ongoing therapy and towards different methods of treatment such as pulsed therapy and combinations that can shorten drug exposure. There is continued debate about what companies should be charging for the drugs. Their arguments for high prices reflect the research and development costs, nonetheless it has been suggested that more than research and development costs are being recouped. It is essential that companies are urged to keep costs down. These novel agents work but in the UK there will be a huge battle with funders. This is a very emotive topic, particularly when patients are in a relapsed refractory state and it

is known that they simply will not survive unless they can be treated with the new drugs; this situation will incite enormous pressure from the treating physicians on the funders to enable access to the necessary drugs. Therefore major challenges lie ahead for patients, clinicians and funding bodies alike.

REFERENCES

1. Shivedel L et al. Conventional dose fludarabine-based regimens are effective but have excessive toxicity in elderly patients with refractory chronic lymphocytic leukemia. Leuk Lymphoma. 2003;44(11);1947-50.

2. Bezares RF et al. Multicenter study of subcutaneous alemtuzumab administered at reduced dose in patients with fludarabine-relapsed/refractory chronic lymphocytic leukemia: final analysis. Leuk Lymphoma. 2011;52(10):1936-41.

3. Marrotta G et al. Low-dose fludarabine and cyclophosphamide in elderly patients with B-cell chronic lymphocytic leukemia refractory to conventional therapy. Haematologica. 2000;85(12):1268-70.

4. Forconi F et al. Low-dose oral fludarabine plus cyclophosphamide in elderly patients with untreated and relapsed or refractory chronic lymphocytic Leukaemia. Hematol Oncol. 2008;26(4):247-51.

5. Eichhorst BF et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009;114:3382-91.

6. Mulligan SP et al. A randomised dose de-escalation safety study of oral fludarabine, ±oral cyclophosphamide and Intravenous rituximab (OFOCIR) as first-line therapy of fit patients with chronic lymphocytic leukaemia (CLL) aged ≥65 years – end of recruitment analysis of response and toxicity of the australasian leukaemia and lymphoma group (ALLG) and CLL Australian research consortium (CLLARC) CLL5 study. Blood. 2012;120:Abstract 463. Presented on 10 Dec 2012, 54th ASH Annual Meeting and Exposition, Georgia, USA.

7. Dartigeas C et al. Safety and efficacy of abbreviated induction with oral fludarabine (F) and cyclophosphamide (C) combined with dose-dense IV rituximab (R) in previously untreated patients with chronic lymphocytic leukemia (CLL) aged > 65 Years: results of a multicenter trial (LLC 2007 SA) on behalf of the french GOELAMS/FCGCLL-WM intergroup. Proc ASH. 2012;Abstract 434. Presented on 10 Dec 2012, 54th ASH Annual Meeting and Exposition, Georgia, USA.

8. Smolej L et al. Low-dose FCR in elderly/comorbid patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): updated results of project q -lite by Czech CLL study group. 2013;Abstract P076. Presented at the 18th Congress of the European Hematology Association, Stockholm, Sweden, June 13-16 2013.

9. Kolibaba KS et al. Demographics, treatment patterns, safety, and real-world effectiveness in patients aged 70 years and over with chronic lymphocytic leukemia receiving bendamustine with or without rituximab: a retrospective study. Ther Adv Hematol. 2013;4:157-71.

10. Knauf WU et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27:4378-84.

11. Fischer K et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012;30(26):3209-16.

12. Fischer K et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011;29:3559-66.

13. Weide R et al. Bendamustine/mitoxantrone/rituximab: a short remission induction chemoimmunotherapy for elderly patients with relapsed or refractory chronic lymphocytic leukemia. Leuk Lymphoma. 2009;50:1468-74.

14. Leblond V et al. Phase II trial in advanced waldenstrom macroglobulinemia (WM) patients with bortezomib: interest of addition of dexamethasone to bortezomib on behalf of the French CLL/WM Intergroup (NCT 00777738). 2012;Poster Presentation 4359,Session 623. Presented on 9 Dec 2012, 55th ASH Annual Meeting and Exposition, New Orleans, USA.

15. Hillman P et al. Rituximab plus chlorambucil in patients with CD20-positive B-cell chronic lymphocytic leukemia (CLL): final response analysis of an open-label phase II study. ASH Annual Meeting Abstracts. Orlando, Florida. 2010;116:Abstract 697.

16. Foa R et al. Rituximab plus chlorambucil as initial treatment for elderly patients with chronic lymphocytic leukemia (CLL): effect of pre-treatment biological characteristics and gene expression patterns on response to treatment. Blood. (ASH Annual Meeting Abstracts). 2011;118:Abstract 294.

17. Goede V et al. Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial. J Clin Oncol. 2013; (suppl; abstr 7004). 2013 ASCO Annual Meeting.

18. CLL11: A study of R05072759 (GA101) with chlorambucil in patients with previously untreated chronic lymphocytic leukemia. www.clinicaltrials.gov (NCT01010061).

19. O'Brien SM et al. The Bruton's Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) is Highly Active and Tolerable in Relapsed or Refractory and Treatment Naive Chronic Lymphocytic Leukemia Patients, Updated Results of a Phase Ib/II Study. 2012;Abstratct 1970. Presented on 16 June, 17th Congress of European Hematology Association, the Netherlands.

20. O'Brien SM et al. A phase II study of the selective phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib (GS-1101) in combination with rituximab (R) in treatment-naive patients (pts) ≥65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). J Clin Oncol. 2013; (suppl; abstr 7005). 2013 ASCO Annual Meeting.

21. Hallek M et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164-74.

22. Fischer K et al. Extended follow up of the CLL8 protocol, a randomized phase-III trial of the German CLL Study Group (GCLLSG) comparing fludarabine and cyclophosphamide (FC) to FC plus rituximab (FCR) for previously untreated patients with chronic lymphocytic leukemia (CLL): results on survival, progression-free survival, delayed neutropenias and secondary malignancies confirm superiority of the FCR regimen. ASH Annual Meeting Abstracts 2012:435.

23. Böttcher S et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the

randomized GCLLSG CLL8 trial. J Clin Oncol. 2012;30(9):980-8.

24. A Phase III study of the efficacy and safety of lenalidomide maintenance for high-risk patients with CLL following first-line therapy. http://clinicaltrials.gov.

25. FCR or BR in patients with previously untreated B-cell chronic lymphocytic leukemia (CLL10). http://clinicaltrials.gov.

26. A safety and efficacy trial of a combination of bendamustine, rituximab and lenalidomid in patients with chronic lymphocytic leukemia (CLL2P). http://clinicaltrials.gov.

27. Byrd JC et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32-42.

28. Burger JA et al. the BTK inhibitor ibrutinib in combination with rituximab is well tolerated and displays profound activity in high-risk CLL patients. 2012;Abstract 187. Presented on 9 Dec 2012, 54th ASH Annual Meeting and Exposition, Atlanta, USA.

29. A study of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. http://clinicaltrials.gov.

30. Chang BY et al. Use of tumor genomic profiling to reveal mechanisms of resistance to the BTK inhibitor ibrutinib in chronic lymphocytic leukemia (CLL). J Clin Oncol. 2013;(suppl; abstr 7014). Presented at 2013 ASCO Annual Meeting.

31. Seymour JF. Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Poster Discussion Session. Leukemia, Myelodysplasia, and Transplantation Track 2013 ASCO Annual Meeting. Abstract No: 7018.

32. Martin D. Betrayal of 20,000 cancer patients: rationing body rejects ten drugs (allowed in Europe) that could have extended lives. Daily Mail. 16 March 2010.

33. NICE briefing paper for the Methods Working Party on the cost-effectiveness threshold. http://www.nice.org.uk/media/4A6/41/CostEffectivenessThresholdFinalPaperTabledAtWPMeeting5Sep3907KT.pdf. Accessed Mar 2013.

34. SMC guidance to manufacturers for completion of new product assessment form. http://www.ispor.org/peguidelines/source/GuidanceinScotland-June2007.pdf. Accessed Mar 2013.

35. NHS guidance for measuring effectiveness and cost effectiveness: the QALY. http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcost-effectivenesstheqaly.jsp. Accessed Mar 2013.

36. Laupacis A et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ. 1992;146(4):473-81.

37. Drummond MF et al. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23(1):36-42.

38. NICE document for appraising orphan drugs. http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf. Accessed Mar 2013.

39. Goede V et al. Cumulative illness rating scale (CIRS) is a valuable tool to assess and weigh comorbidity in patients with chronic lymphocytic leukemia: results from the CLL8 trials of the German CLL Study Group. Haematologica. 2012;97(S1):154.

40. UK Life Tables 2005-2007.

41. Thurmes P et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2008;49(1):49-56.

42. Cramer P et al. Impact of different chemotherapy regimen in comorbid patients with advanced chronic lymphocytic leukemia: Meta analysis of two phase-III-trails of the German CLL Study Group. Blood. 2006;108:a2840.

43. Laurance J. The real cancer killer: rip-off prices for drugs. The Independent. 29 April 2013.

44. Leukaemia incidence statistics. Cancer Research UK.

EXTREME HYPOFRACTIONATED IMAGE-GUIDED RADIOTHERAPY FOR PROSTATE CANCER

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ABSTRACT

An emerging body of data suggests that hypofractionated radiation schedules, where a higher dose per fraction is delivered in a smaller number of sessions, may be superior to conventional fractionation schemes in terms of both tumour control and toxicity profile in the management of adenocarcinoma of the prostate. However, the optimal hypofractionation scheme is still the subject of scientific debate. Modern computer-driven technology enables the safe implementation of extreme hypofractionation (often referred to as stereotactic body radiation therapy [SBRT]). Several studies are currently being conducted to clarify the yet unresolved issues regarding treatment techniques and fractionation regimens. Recently, the American Society for Radiation Oncology (ASTRO) issued a model policy indicating that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low-to-intermediate risk disease. The present article reviews some of the currently available data and examines the impact of tracking technology to mitigate intra-fraction target motion, thus, potentially further improving the clinical outcomes of extreme hypofractionated radiation therapy in appropriately selected prostate cancer patients. The Champalimaud Centre for the Unknown (CCU)'s currently ongoing Phase I feasibility study is described; it delivers 45 Gy in five fractions using prostate fixation via a rectal balloon, and urethral sparing via catheter placement with on-line intra-fractional motion tracking through beacon transponder technology.

Keywords: Prostate cancer, radiation therapy, hypofractionated, hypofractionation, IGRT, beacon transponders.

INTRODUCTION

External beam radiation therapy given with conventional fractionated schedules (1.8-2 Gy daily) to a total dose of 78-86 Gy is an effective definitive treatment modality for all risk groups of prostatic adenocarcinoma. Patients are classically stratified according to their biopsy Gleason score, serum prostate-specific antigen (PSA) level, and clinical stage, and defined as: low-risk, clinical stage T1c and T2a, PSA level ≤10 ng/mL, and biopsy Gleason score ≤6; intermediate-risk, clinical stage T2b or biopsy Gleason score of 7 or PSA level >10 and ≤20 ng/mL; high-risk, clinical stage ≥T2c or PSA level >20 ng/mL or biopsy Gleason score ≥8. A great deal of scientific debate revolves around the optimal choice of treatment strategy for all risk categories, and, more specifically, about the choice of radiation modality and the role of androgen ablation therapy in selected patient groups.[1]

Multiple randomised Phase III studies have confirmed the utility of dose escalation in prostate cancer by improving local control, freedom from biochemical failure, and freedom from distant metastases. However, conventional fractionation schedules do not permit further escalation beyond doses currently used because of unacceptably high rates of acute and late toxicities using 3D-conformal techniques. Recently, radiotherapy has witnessed the introduction of major technological advances, which have permitted the implementation of intensity modulated radiotherapy (IMRT). IMRT is a further advancement in 3D-conformal radiotherapy. Its

primary advantage, compared to conventional 3D-conformal treatment techniques, is the ability to produce very sharp dose gradients and to deliver highly conformal target doses with better sparing of normal structures. The benefits of IMRT delivery are particularly pronounced in the context of concave-shaped target-critical structure geometries and, in the treatment of localised prostate cancer, its implementation has resulted in improved toxicity profiles using conventional fractionation regimens.[2]

Current research efforts are aimed at the incorporation of high-quality imaging in the radiotherapy process, both at the level of target volume delineation, with the use of state-of-the-art imaging modalities (e.g. magnetic resonance imaging [MRI]) for accurate morphological identification of the target volume and, at treatment delivery, with the specific aim to minimise uncertainties and reduce exposure to normal tissues. This process is commonly referred to as image-guided radiation therapy (IGRT). The ultimate goal of IGRT, of course, is that radiation dose can be delivered to an accurately defined target volume exactly as planned. Indeed, 3D volumetric imaging tools for near real-time verification of target position (on-board imaging devices) are now available, and appropriate correction strategies are rapidly being developed.

Dose-limiting toxicities observed with conventional fractionation as well as the extremely protracted length of the treatment (up to 8-9 weeks) have been recently challenged through the advent of improved technology. This has led to the investigation of new approaches with hypofractionated regimens that would deliver the same or higher biologically-equivalent tumour dose in fewer sessions while maintaining or decreasing toxicity rates. An emerging body of data suggests that mildly hypofractionated radiation schedules (with dose per fraction up to 4 Gy), where treatment is delivered more quickly and conveniently, do not compromise biochemical control or toxicity, so long as careful treatment planning and delivery techniques are adopted.[3-5] Schemes adopting between 20 and 28 sessions have become established in the clinical practice and are currently routinely employed, largely through the adoption of IMRT plans with tighter safety margins to account for organ motion, based on patient set-up techniques which enhance inter-fraction reproducibility. Three ongoing multi-institutional non-inferiority trials in patients with low and intermediate-risk treated with contemporary dose prescription, planning, and delivery techniques will soon shed light on the potential advantages of moderate hypofractionation over conventional fractionation. A preliminary report on late toxicity with over 4 years median follow-up in one of these studies indicates similar side-effects regardless of treatment regimen with less than 5% Radiation Therapy Oncology Group (RTOG) rectal toxicity and less than 3% RTOG bladder toxicity.[4]

THE CASE FOR EXTREME HYPOFRACTIONATION

Extreme hypofractionated image-guided radiotherapy, sometimes referred to as stereotactic body radiotherapy (SBRT), or stereotactic ablative radiotherapy (SABR), aims to deliver even fewer high doses of radiation to the target volume with extreme accuracy and conformity. Growing radiobiological evidence indicates that prostate cancer may have a greater sensitivity to large dose per fraction compared to the surrounding normal tissues due to its generally very low alpha/beta ratio, generally believed to be as low as 1.5. Therefore, a potential increase in the therapeutic ratio may be achieved through extreme hypofractionation where the biologically effective dose (BED) to the target tissues is enhanced, while a reduction in the risk of radiation-induced complications may be expected.[6,7] Furthermore, ultra-high dose per fraction may differ from moderate hypofractionation in terms of cell kill with laboratory as well as clinical evidence suggesting a direct effect on the endothelial cell and tumour vasculature.[8]

In recent years, clinical outcomes supporting the safety and increasingly longer-term efficacy of extreme hypofractionation have been published. Initially, extreme hypofractionation was performed by means of high-dose rate (HDR) brachytherapy. In the 1990's this approach was shown to yield excellent tumour control with reasonably low morbidity. In one study, 5-year freedom from biochemical failure rates of 91% and 88% were reported in low-risk patients treated using a total dose of 38 Gy delivered in four fractions, or 42 Gy delivered in six fractions, respectively.[9] However, HDR brachytherapy entails hospitalisation and anaesthesia and is uncomfortable for the patient particularly for multi-day delivery regimens

where needles remain inserted into the patient for an extended time period.

The advent of image-guided delivery technologies in the early 2000's with their improved accuracy rapidly opened the doors for high-dose external beam delivery. To date, only a few publications have reported on the clinical outcomes of external-beam extreme hypofractionated delivery and no data from randomised studies are yet available.[10-13] The first prospective experience using ultra-high dose external-beam SBRT was reported by the Stanford University group. In this Phase II clinical trial, 41 low-risk, hormone naïve patients received a dose of 36.25 Gy delivered in five fractions.[11] CT scans were only used for treatment planning. The planning target volume (PTV) was identified with the prostate only with a 5 mm margin all around, except posteriorly where a 3 mm margin was used. The prescribed dose was normalised to the 90% isodose line. At a median follow-up of 33 months, no failures were noted. At median 5-years follow-up the actuarial freedom from biochemical failure was 94%. However, Grade 2 and Grade 3 late GU toxicity was observed in 7% and 2.5% of cases, respectively.[14] In a recent dose escalation study, three groups of 15 patients each received either 45 Gy, 47.5 Gy, or 50 Gy (the regimen with the highest dose reported to date) delivered in five fractions every other day.[10] If prostate cancer has, indeed, an alpha/beta ratio of 1.5, and if the extrapolation with the linear-quadratic formalism holds for such high-dose per fraction, the biologically equivalent doses to the tumour with 2 Gy per fraction would be 135, 149, and 164 for the three dose levels, respectively.[15] Undoubtedly, this trial has tested the limits of hypofractionated dose escalation for prostate cancer. A great deal of care was used to minimise treatment uncertainties. A rectal balloon was used to push the posterior and lateral rectal walls away from the PTV and to stabilise the prostate. Fiducial markers and cone-beam CT were used for daily set-up, but intra-fraction guidance was not used. A 3 mm expansion of the clinical target volume (CTV) was used to create the PTV. Median follow-up was 30, 18, and 12 months for the 45, 47.5, and 50 Gy groups, respectively. Overall, genito-urinary (GU) Grade 2 and Grade 3 toxicity occurred in 31% and 4% of patients, respectively, and one case of Grade 4 GU toxicity was reported at the highest dose level. Rectal Grade 2 and Grade 3 toxicity was found in 18% and 2% of patients, respectively. Biochemical control was 100% with a mean PSA of 0.2 ng/mL at 30 months.

The largest prospective study of extreme hypofractionation comes from Winthrop University Hospital and includes 304 patients; mostly comprising low and intermediate-risk disease.[16] The study has reached a 5-year median follow-up for patients who received a prescription dose of 36.25 Gy in five daily sessions of 7.25 Gy. No patients experienced Grade 3 complications and fewer than 5% had Grade 2 rectal or urinary morbidity. Bowel and urinary quality of life (QoL) scores initially decreased, but later returned to baseline values. An overall decrease of 20% in the sexual QoL score was observed. For patients that were potent prior to treatment, 75% remained sexually active. Actuarial 5-year biochemical recurrence-free survival was 97% for low-risk, 90.7% for intermediate-risk.

Recently a multi-institutional pooled analysis with 1,100 cases from prospective Phase II studies has been published.[17] The 5-year biochemical relapse free survival (bRFS) rate was 93% for all patients and 95%, 84%, and 81% for low, intermediate and high-risk patients, respectively ($p<0.001$). For 135 patients possessing a minimum of 5-years follow-up, the 5-year bRFS rate for low and intermediate-risk patients was 99% and 93%, respectively.

Table 1 summarises the published studies on extreme hypofractionation. Toxicity appears acceptable, largely consisting of Grade 2 side-effects. Freedom from biochemical failure looks extremely promising and compares favourably with other definitive treatments for low and intermediate-risk patients. Currently available evidence supports consideration of extreme hypofractionation among the therapeutic options for low and intermediate-risk patients. Randomised trials involving extreme hypofractionation are currently ongoing. For instance, RTOG 0938 is actively recruiting low-risk patients and randomises between 36.25 Gy in five fractions versus 51.6 Gy in 12 sessions of 4.3 Gy in 2.5 weeks in both arms.

TREATMENT SAFETY, REPRODUCIBILITY AND ORGAN MOTION MANAGEMENT

Safe delivery of extreme hypofractionated treatments mandates the fulfillment of strict

Table 1. Extreme hypofractionation studies.

Author (ref)	Year	Patient number	Risk category	Median FU (months)	Fractionation Regimen	Grade ≥2 Toxicity	bRFS %
Friedland et al.[12]	2009	112	Low Intermediate – High	24	35 Gy (7 Gy x 5)	GU=6 GI=1%	97%
Boike et al.[10]	2011	45	Low (40%) Intermediate (60%)	30	45 Gy (9 Gy x 5) 47.5 Gy (9.5 Gy x5) 50 Gy (10 Gy x 5)	GU=31% GI=18%	100%
King et al.[14]	2012	67	Low Intermediate	32	36.25 Gy (7.25 Gy x 5)	GU=8.5 GI = 2	94%
McBride et al.[13]	2012	45	Low	44.5	37.5Gy (7.5 Gy x 5) or 36.25 Gy (7.25 Gy x 5)	Gu=19% GI=12%	97.7%
Katz et al.[16]	2013	304	Low (69%) Intermediate (27%) High (4%)	60	37.5Gy (7.5 Gy x 5) or 36.25 Gy (7.25 Gy x 5)	GU<5% GI<5%	97% (low-risk) 90.7% (intermediate) 74.1% (high)
King et al.[17]	2013	1100	Low (58%) Intermediate (30%) High (11%)	36	36.25 Gy (7.25 Gy x 5)		93% (overall) 95% (low-risk) 84% (intermediate) 81% (high)

bRFS: biochemical relapse-free survival; GU: genitourinary; GI: gastrointestinal.

dose/volume constraints to the adjacent normal tissues, namely the bladder and rectal walls, as well as the urethra, genito-urinary diaphragm, and penile bulb. Urethral sparing, in particular, may be difficult to achieve due to the inability to identify the organ on conventional CT planning without the aid of a catheter, and for the large variability in its anatomical position. Advanced imaging modalities including multiparametric MRI with CT fusion ought to be adopted to improve target volume and organ-at-risk contouring, and further exploit the potential benefits of the dose-painting capabilities of modern treatment-planning software. Moreover, due to the high-dose gradients of IMRT plans, measures to mitigate inter and intra-fraction movement of the prostate ought to be adopted. Inter-fraction motion has been extensively studied both with implanted radiopaque fiducials and electromagnetic beacon transponder technology.[18-20] Intra-fractional motion has been shown to be significant, especially in the dorso-ventral axis where >3 mm shifts may be observed within minutes of cone-beam CT (CBCT) matching with the planning CT. In a recent study, in which electromagnetic transponders were used for daily patient set-up followed by CBCT, with a prescription dose of 40 Gy delivered in five fractions, at a median follow-up of 36 months, no biochemical failures were found. At 18 months, the mean Expanded Prostate Cancer Index Composite (EPIC) scores for bowel, urinary, and sexual function showed no significant changes from baseline.[19] The electromagnetic transponder technology allows continuous detection of prostate translations, which, when coupled with manual intervention, permits correction of patient positioning. Through the aid of a six degrees of freedom couch capable to adjust for translational as well as rotational shifts in quasi real-time as they are detected by the device, these uncertainties may be further reduced. Additionally, measures to mitigate intra-fractional

Figure 1.a

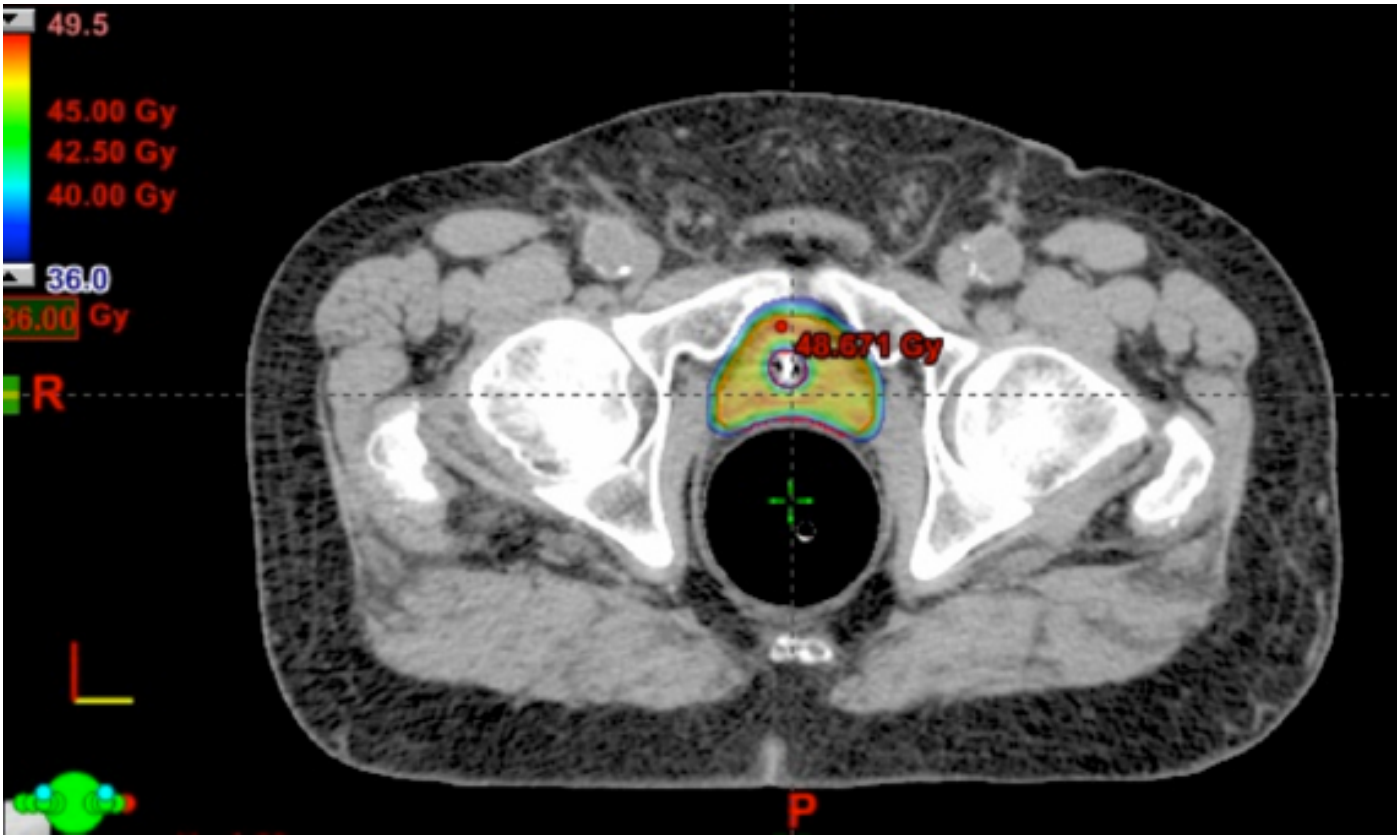

Figure 1.b

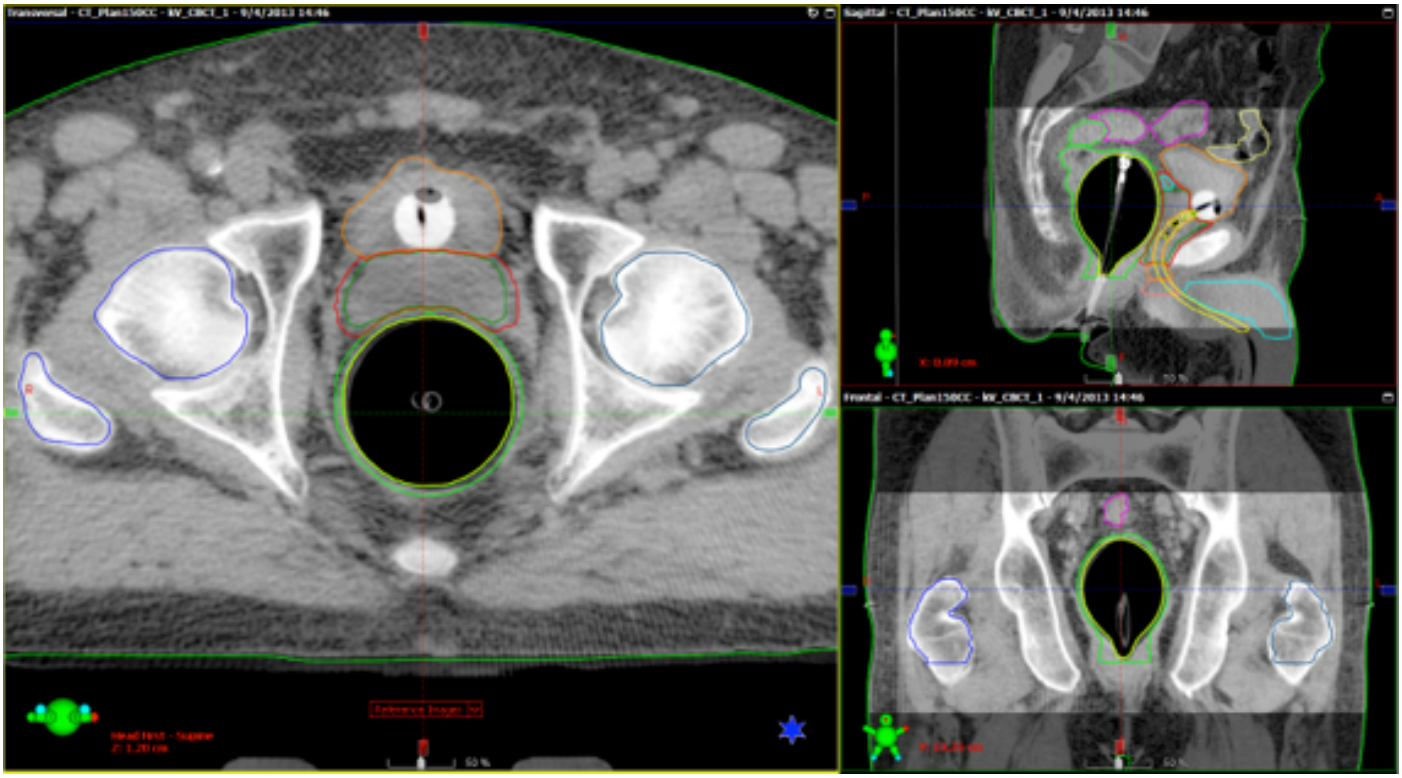

Figure 1. Dose distribution for the extreme hypofractionation protocol used at CCU.
The dose distribution to the target volume includes the whole prostate and seminal vesicles. The rectal balloon is filled with 150 cc of air to fix the anatomy, and the urethral catheter with transponders is used to identify and track the location of the urethra.
Figure 1a. Axial plane with dose distribution.
Figure 1b. Cone-beam CT (CBCT) and planning reference CT match show excellent anatomical correlation immediately prior to treatment delivery on the axial, sagittal and coronal planes.

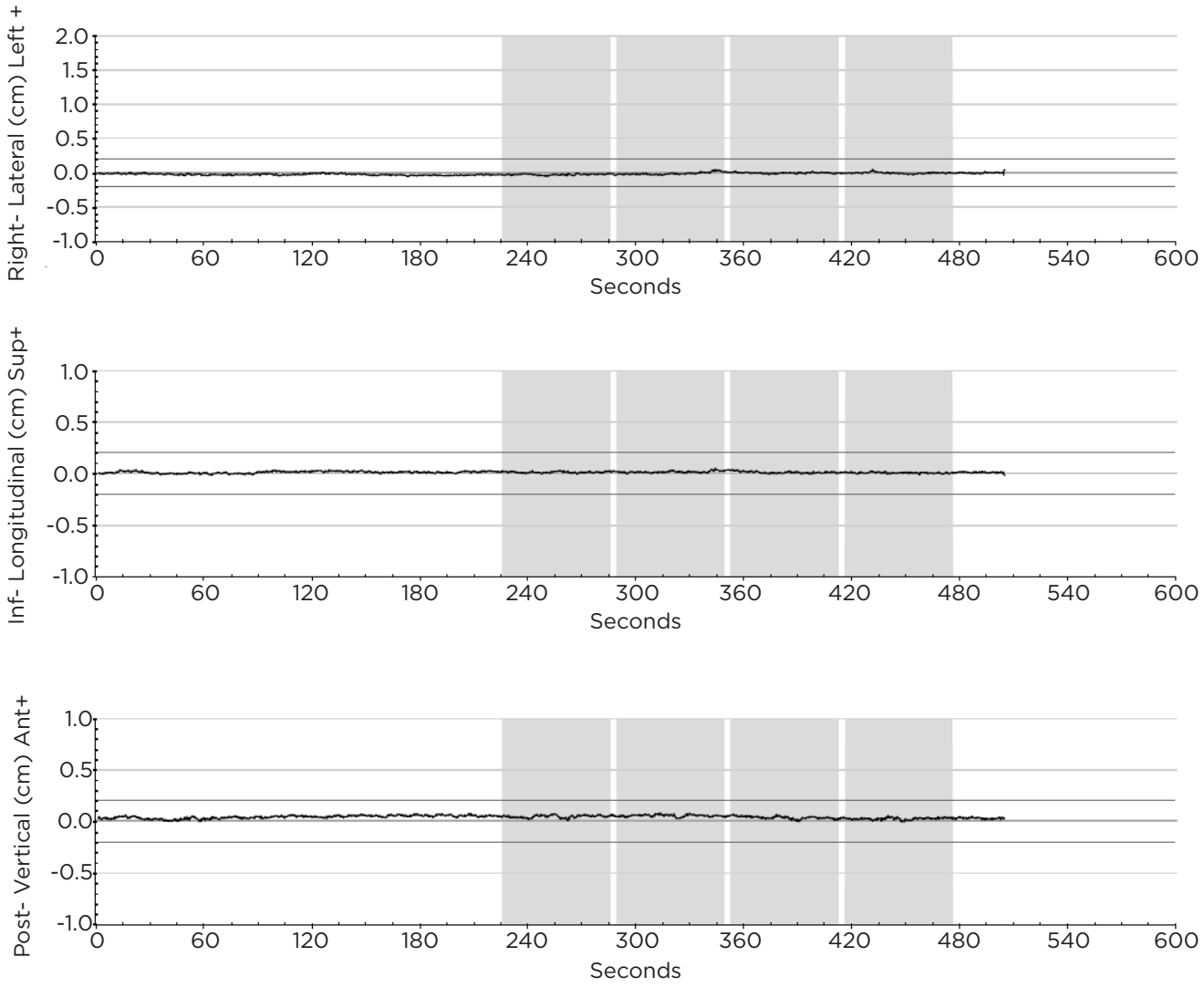

Figure 2. Treatment report for a treatment session of 9 Gy using beacon transponder technologies. Deviation from the reference location of the target is shown for the lateral, longitudinal and vertical axis, respectively (from top to bottom). Maximum displacement during the entire session is <1 mm. The four vertical grey bands correspond to actual beam-on for four consecutive arcs using VMAT with a 10 MV FFF beam.

motion of the prostate and create anatomical reproducibility of the rectum may be adopted by the use of endorectal balloons whose efficacy has been widely documented.[21-23] The accomplishment of urethral sparing via negative dose-painting to minimise GU toxicity is feasible through appropriate imaging procedures and via on-line tracking during treatment delivery. MRI image-fusion allows the identification of critical structures such as the neurovascular bundles and the penile bulb which may be electively spared from high-dose radiation with the intent to potentially reduce the incidence of radiation-induced erectile dysfunction.[24]

PHASE I FEASIBILITY STUDY AT CCU

At the Champalimaud Centre for the Unknown (CCU), Lisbon, Portugal, great emphasis has been placed in the accuracy of patient simulation, planning, and set-up procedures to maximise the potential benefits of extreme hypofractionation in selected cases. A Phase I feasibility study of a prescription dose of 45 Gy in 9 Gy sessions delivered every other day has just been concluded. MRI and CT simulations for planning have been performed with endorectal balloons. The optimal balloon volume as a function of the patient's specific anatomy is the subject of current investigation. Excellent anatomical reproducibility and target stabilisation at the time

of treatment have been confirmed for volumes ≥100 cc. Rectal wall, urethral, genito-urinary diaphragm, and penile bulb sparing are achieved via the fulfillment of strict dose-volume constraints. Set-up reproducibility prior to treatment delivery is monitored via intraprostatic electromagnetic beacon transponders and accurate anatomical matching is verified via CBCT immediately prior to a fast flattening filter-free (FFF) beam delivery. Electromagnetic transponder intra-fractional tracking has shown <1 mm variation in all directions during treatment delivery. 10 patients with low and intermediate-risk disease have completed treatment in this Phase I study and are currently being monitored for treatment-related toxicity using validated EPIC questionnaires for the GU, GI, and sexual domains. With a median follow-up of 3 months, no acute Grade 2 GU and GI toxicities have been observed so far. The feasibility of neurovascular bundle sparing is currently being investigated in selected cases. Figure 1 shows the dose distribution to the target volume to 45 Gy in five sessions. The target volume includes the whole prostate and seminal vesicles. The rectal balloon with 150 cc filling of air is used to fix the anatomy, and the urethral catheter with transponders is essential to identify and track the location of the urethra during treatment as performed in the CCU protocol. Figure 2 shows the treatment session report of measured motion using beacon transponder technology as used at CCU, indicating <1 mm deviation from the reference for the entire duration of the treatment.

CONCLUSION

Preliminary data convincingly indicate that extreme hypofractionation holds great promise of achieving excellent biochemical relapse-free outcomes in properly selected prostate cancer patients. Preliminary experiences with extreme hypofractionation are maturing, and randomised studies comparing moderate versus ultra-high dose regimens are currently being carried out. Recently, ASTRO has issued a model policy indicating that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an alternative for appropriately selected patients with low to intermediate-risk disease.[25] However, great emphasis on rigorous planning and delivery techniques must be placed when using extreme hypofractionated regimens to fully exploit their potential benefits in optimising the therapeutic ratio, thus yielding optimal uncomplicated clinical outcomes.

REFERENCES

1. D'Amico A et al. Prostate cancer: where we have been, where we are, and where we are going. Semin Radiat Oncol. 2013;23:155-6.

2. Zelefsky MJ et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol. 2006;176:1415-9.

3. Kupelian PA et al. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. Int J Radiat Oncol Biol Phys. 2007;68:1424-30.

4. Dearnaley D et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol. 2012;13:43-54.

5. Arcangeli G et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2010;78:11-8.

6. Brenner DJ et al. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys. 2002;52:6-13.

7. Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncol. 2005;44:265-76.

8. Fuks Z et al. Engaging the vascular component of the tumor response. Cancer Cell. 2005;8:89-9.

9. Martinez AA et al. High-dose-rate prostate brachytherapy: an excellent accelerated hypofractionated treatment for favorable prostate cancer. Am J Clin Oncol. 2010;33:481-8.

10. Boike TP et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. J Clin Oncol. 2011;29:2020-6.

11. King CR et al. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys. 2009;73:1043-8.

12. Friedland JL et al. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. Technol Cancer Res Treat. 2009;8:387-92.

13. McBride SM et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. Cancer. 2012;118:3681-90.

14. King CR et al. Long-Term Outcomes from a Prospective Trial of Stereotactic Body Radiotherapy for Low-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2012;82:877-82.

15. Cabrera AR et al. Hypofractionation for clinically localized prostate cancer. Semin Radiat Oncol. 2013;23:191-7.

16. Katz AJ et al. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. Radiat Oncol. 2013;8:118.

17. King CR et al. Stereotactic body

radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol. 2013 [Epub ahead of print].

18. Kron T et al. Intra-fraction prostate displacement in radiotherapy estimated from pre- and post-treatment imaging of patients with implanted fiducial markers. Radiother Oncol. 2010;95:191-7.

19. Hossain S et al. Simulated real time image guided intrafraction tracking-delivery for hypofractionated prostate IMRT. Med Phys. 2008;35:4041-8.

20. Kupelian P et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys. 2007;67:1088-98.

21. Teh BS et al. The use of rectal balloon during the delivery of intensity modulated radiotherapy (IMRT) for prostate cancer: more than just a prostate gland immobilization device? Cancer J. 2002;8:476-83.

22. Sanghani MV et al. Impact on rectal dose from the use of a prostate immobilization and rectal localization device for patients receiving dose escalated 3D conformal radiation therapy. Urol Oncol. 2004;22:165-8.

23. van Lin EN et al. Rectal wall sparing effect of three different endorectal balloons in 3D conformal and IMRT prostate radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63:565-76.

24. Wiegner EA et al. Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. Int J Radiat Oncol Biol Phys. 2010;78:442-8.

25. American Society for Radiation Oncology (ASTRO) SBRT Model Policy. https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/2013HPcoding%20guidelines_SBRT_Final.pdf

PROSTATE CANCER AND INFLAMMATION: THE ROLE OF miRNAs

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ABSTRACT

Approximately 15-20% of all human cancers are assumed to be a result of infection and chronic inflammation due to a constant supply of cytokines and reactive oxygen species, giving rise to genomic instability and a subsequent tumour development. In recent years, chronic inflammation has also been hypothesised to influence prostate carcinogenesis, since both acute and chronic inflammation is commonly seen in prostatic tissues. The signalling pathways involved in the immune response and tumour development are overlapping with each other, and it has been proposed that miRNAs are a possible link between the two processes. In this review, we are describing some of the miRNAs which could constitute a conceivable link between inflammation and prostate cancer.

Keywords: Prostate cancer, inflammation, microRNAs.

PROSTATE CANCER

Prostate cancer (PCa) is the most common malignancy among men in Western society. In 2012, almost 360,000 new cases of PCa were diagnosed in the European Union, and 71,000 men died from the disease.[1] Even though PCa is a very common disease, the aetiology is largely unknown. The most established risk factors are family history, age, and African-American ethnicity, although chronic inflammation and infection have also been suggested to play a role in prostate carcinogenesis.[2]

INFLAMMATION-RELATED CANCER

Inflammation was linked to cancer more than a century ago by Rudolf Virchow who observed inflammatory cells in tumour specimens and found that tumours often developed in close vicinity to chronic inflammation.[3] The inflammation could not be exclusively explained as an anti-tumour immune response since it is often scattered throughout an entire organ and it is also commonly seen in pre-lesions to cancer. Today, approximately 15-20% of all human cancers in adults are suggested to result from infection and chronic inflammation.[4] Classic examples of malignancies where inflammation are considered a risk factor are colon cancer arising in individuals with inflammatory bowel disease, and gastric cancer caused by *Helicobacter pylori* infections.[5]

Inflammation is a process that involves both an innate and adaptive immune response following infection or injury. The innate immune system initiates the inflammatory response by producing a large number of cytokines, reactive oxygen (ROS), and nitrogen species (RNS).[6] This process is essential, not only to eliminate pathogens and repair tissue damage, but also to activate the adaptive immune response. Even though inflammation acts as a host defence and usually is a self-limiting process, failure leading to inadequate resolution of inflammatory responses may be pathologically conductive. Chronic inflammation has been linked to tumour promotion and progression by several mechanisms, including increased cell proliferation, enhanced

angiogenesis, and evasion from apoptosis. A constant supply of cytokines, ROS, and RNS in a microenvironment with sustained inflammation may, over time, give rise to genomic instability and subsequent tumour development.[7]

MicroRNAs

MicroRNAs (miRNAs) are small non-coding RNA molecules with a size of 18-24 nt, whose function is to post-transcriptionally regulate genes involved in a wide range of biological processes, such as differentiation, apoptosis, and inflammation.[8,9] Studying the effect of miRNAs in the human genome is complicated due to the fact that one miRNA could regulate the expression of several target genes, and one gene could be regulated by several miRNAs. Furthermore, different miRNAs are expressed in different cell types, and the miRNAs expressed in one cell type could have expression levels that differ up to 1,000-fold across the differentiation stages of that cell.[10] Even though the expression of a miRNA does not change within a cell, it could have different functions between the different differentiation stages within that cell.

Several large-scale studies investigating the miRNA expression patterns in PCa have been performed to date, although the results from these studies are inconclusive with some studies reporting miRNAs to be up-regulated while others report them as down-regulated or not deregulated at all.[11-17] This inconsistency between study results could be due to the study material and method used, but it could also be due to the heterogeneous nature of PCa and tumour development or the complexity of the miRNA system.

miRNAs, INFLAMMATION AND PROSTATE CANCER

It is now well-known that miRNAs are involved in almost all inflammatory responses and that they have a significant impact on the magnitude of the inflammatory response. This is accomplished by influencing the development of inflammatory cells, establishing the level of immune cell function and cytokine production, as well as responding when the immune system encounters pathogens. By activation and repression of multiple miRNAs, the capacity of the immune system is properly balanced, creating a fine-tuned system.[18] A properly adjusted miRNA expression results in a transient inflammatory response that clears the infection without causing any damage to the host tissue. Deregulation of miRNA expression could result in either an immunodeficiency or a hyperactive response to infection, which could be extremely harmful. A constant deregulation of miRNA expression could also lead to a chronic inflammatory state. There are a vast number of miRNAs playing crucial roles in the inflammatory response, of which miR-146a, miR-21 and miR-155 are among the most well-described in the literature today. A summary of the regulatory functions of these miRNAs on the inflammatory response can be seen in Figure 1.

miR-146a

MicroRNA-146a (miR-146a) has been proposed to play a role in regulating toll-like receptor (TLR) signalling in response to bacterial pathogens by preventing excessive inflammation. Thus, the role of miR-146a is to dampen the production of pro-inflammatory mediators such as IL-6 and TNF-α, serving as a negative regulator of the immune system.[19,20] miR-146a is activated in immune cells through cell-surface TLRs (TLR-2, -4 and -5) sensing bacterial pathogens or in response to the pro-inflammatory cytokines IL-1β and TNF-α.[21] This up-regulation occurs when NF-κB binds and trans-activates the gene promoter of miR-146a, leading to activation and subsequent repression of miR-146a target genes, TRAF6 and IRAK1, involved in the TLR/NF-κB pathway.[19-21] Other validated target genes of miR-146a are cyclooxygenase 2 (COX-2) and IL-6, and a down-regulation of miR-146a leads to an increased expression of both of these genes.[22] COX-2 is a key enzyme in the conversion of arachidonic acid to prostaglandins (PGs), and the expression of COX-2 has been found to be elevated in a variety of cancers, for example, breast and prostate. High levels of COX-2 lead to an increased synthesis of PGs, which in turn is believed to contribute to cancer pathogenesis, mainly due to their effect on cell proliferation, angiogenesis, and apoptosis. There are only a few reports on the expression of miR-146a in PCa, stating that a reduced expression of miR-146a is associated with PCa.[14,23]

miR-21

MicroRNA-21 (miR-21) is another miRNA which is induced by NF-κB during TLR-4 signalling. Once activated, this miRNA targets and represses the

pro-inflammatory PDCD4, enhances the production of the anti-inflammatory cytokine IL-10, as well as decreasing the pro-inflammatory activity of NF-κB, thus constituting another negative feedback loop that mutes the immune response.[24] Enhanced levels of IL-10 have been suggested to have an impact on anti-tumour immunity, since IL-10 together with TGF-β are able to expand the population of regulatory T cells (Tregs), which have a suppressive function on CD4/CD8 effector T-lymphocytes, thereby promoting tumour growth. miR-21 has been validated as an oncogene and it is one of the most frequently up-regulated miRNAs in solid tumours including PCa where it promotes survival, anchorage-independent growth, and proliferation.[14,17,25]

miR-155

MicroRNA-155 (miR-155) is one of the best characterised miRNAs to date and it has been implicated to play a role in both the innate and adaptive immune system, as well as in the development of immune cells. This is a pro-inflammatory miRNA which regulates the immune system through the help of a wide range of inflammatory factors such as cytokines and components of the NF-κB pathway. miR-155 targets and down-regulates SHIP1 and SOCS1, leading to an increased activation of Akt and IFN pathways, thus mediating cell survival, growth, and migration.[26,27] miR-155 is also induced through TLRs sensing bacterial and viral pathogens, by TNF-α and through NOD2 sensing bacterial peptidoglycan, suggesting that it is a key player in the immune response towards a broad range of inflammatory mediators.[28,29] Elevated levels of miR-155 lead to increased levels of pro-inflammatory factors, but it has also been shown to lead to an enhanced rate of spontaneous mutations, since miR-155 also targets components of the DNA mismatch repair machinery. If an inflammation becomes chronic, the rate of spontaneous mutations could increase further, and together with a simultaneously miR-155 driven suppression of tumour suppressor genes such as TP53BP1, this could shorten the series of steps required for carcinogenesis.[30,31]

miR-155 has been found to be deregulated in several types of cancer, such as breast cancer[32] and pancreatic cancer,[33] although to our knowledge there are no reports on deregulation in PCa tissues but unpublished results from our group show that miR-155 are up-regulated in the PCa cell line LNCaP (Carlsson et al., Unpublished results).

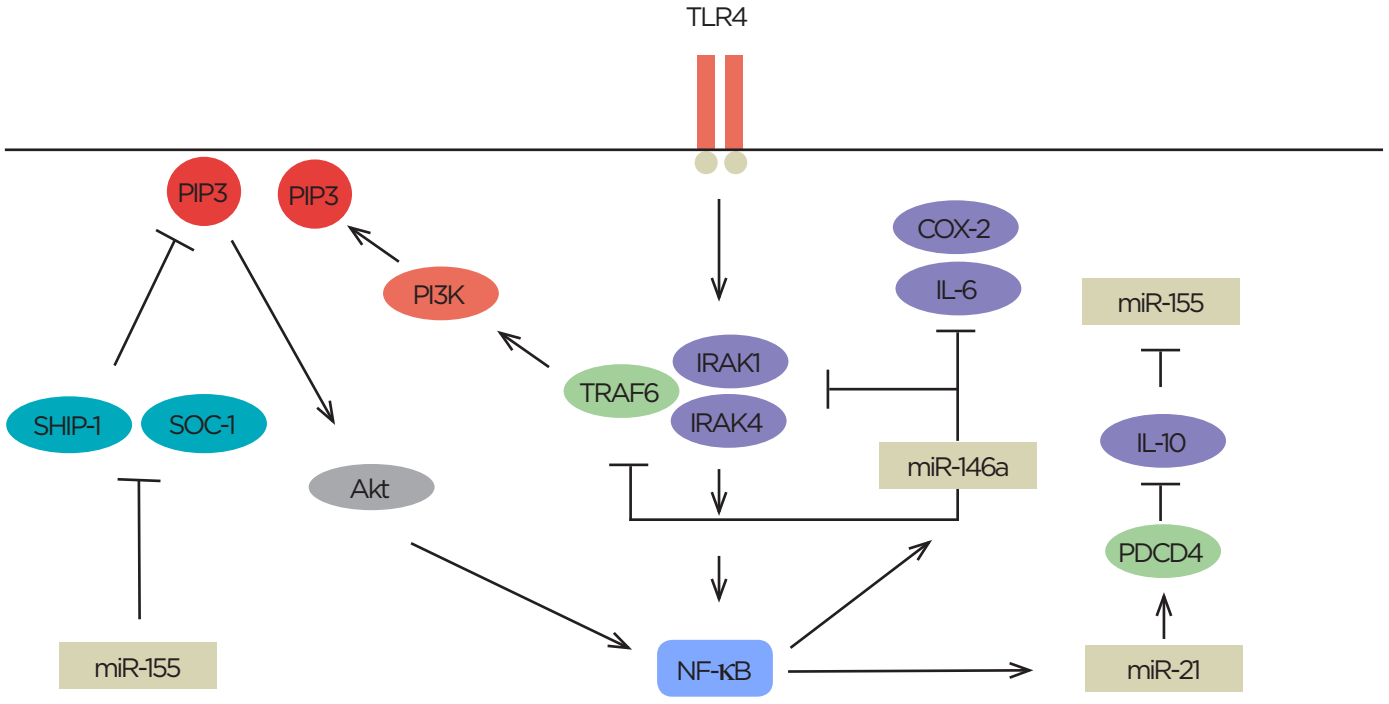

Figure 1. A schematic overview of the regulatory effects of miR-146a, miR-155 and miR-21 on the inflammatory response.

CONCLUDING REMARKS

Nowadays it is well-known that the signalling pathways that are involved in the immune response and inflammation are overlapping with the pathways involved in tumour development, and it has been suggested that it is the expression of miRNAs that links these two processes together.[34] Although, exactly how miRNAs link inflammation and tumour development together, is currently unknown. Thus, the main question is; is it a deregulation of miRNAs (such as miR-155 overexpression and down-regulation of miR-146a) that leads to a chronic inflammation, creating a microenvironment that favours tumour development, or is it a chronic inflammation that leads to a deregulated miRNA expression, which in turn could favour a tumour development?

When performing a literature review, three interesting miRNAs in the context of inflammation and cancer emerge, miR-146a, miR-21 and miR-155. The most interesting of these is miR-146a, which has been found to be deregulated in previous miRNA expression studies in PCa. The role of miR-146a is to dampen the production of pro-inflammatory mediators, a down-regulation of miR-146a leads to increased levels of these mediators, which could result in a chronic inflammation and thus a tumour-stimulating microenvironment. In addition, it could also result in a constant activation of NF-κB, which has been found in several cancers including PCa. NF-κB might be linked to tumour development through induction of pro-inflammatory cytokines, such as IL-6, TNF-α, and COX-2, and may also contribute to genomic instability by promoting release of ROS and RNS. Consequently, a down-regulation of miRNA-146 may have an essential role in early-stage cancer development. If this down-regulation of miR-146a is found together with an elevated level of miR-155, this could increase the risk for tumour development since increased miR-155 levels lead to an enhanced production of pro-inflammatory mediators as well as an enhanced mutation rate. Furthermore, deregulated miRNAs may also participate in later stages of the prostate carcinogenesis. The up-regulation of miR-21 seen in PCa and the subsequently increased levels of IL-10 are suggested to have an impact on the anti-tumour immunity. Evidence has been provided showing that IL-10 and TGF-β are able to expand the Treg population and thereby aid tumour growth. Our group has recently found that men with greater numbers of Treg in their prostate tumour environment have an increased risk of dying of PCa.[35]

Another aspect of the link between miRNAs, inflammation and cancer is infectious agents, and even though host miRNAs are important in the response against infectious pathogens, there are also some pathogens that benefit from the host's miRNAs in their pathogenesis. One such example is Marek's disease, where host miR-155 is essential for the oncogenic potential of the pathogen, thus demonstrating a link between inflammation and cancer following infection.[20] The expression of miRNAs have also been established as a link between infection and the development of cancer in a recent study performed on gastric cancer, where patients with a polymorphism in miR-146a in combination with a Helicobacter pylori infection had a higher risk for developing cancer.[36] It is believed that this polymorphism in the precursor of miR-146a could reduce the production of mature miR-146a, thus leading to a modified inflammatory process where the patient becomes more vulnerable to infections. The same polymorphism has also been found in patients with PCa and was then associated with a higher risk of developing PCa.[37] Even though there have not been any studies investigating whether the risk for PCa is further increased if the polymorphism is found in combination with an infectious agent, it could be hypothesised that this is the case. It is important to keep in mind that not all chronic inflammation in the prostate leads to tumour development. However, in the cases where inflammation does lead to tumour development, it could be hypothesised that it is genetic changes in miRNAs, such as a polymorphism in miR-146a, which predispose these men to PCa development caused by a chronic inflammation. To date, there are no specific infectious pathogens associated with PCa, although the results from other studies suggests that miRNAs could be an important part of any infectious agent's mechanism of infection and its oncogenic potential in PCa as well.

Based on the literature, we suggest that deregulation of inflammatory associated miRNAs, such as miR-146a, miR-21 and miR-155, have the capacity to influence both PCa initiation and progression. To our knowledge, there are no

miRNA expression studies published where the PCa cases studied had a confirmed inflammation (neither acute nor chronic). In order to validate the hypothesised connection between miRNAs, inflammation, and PCa, more studies need to be performed with the specific purpose to study this link.

REFERENCES

1. Ferlay J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49:1374-403.

2. Davidsson S et al. Inflammation, focal atrophic lesions, and prostatic intraepithelial neoplasia with respect to risk of lethal prostate cancer. Cancer Epidemiology, Biomarkers & Prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2011;20:2280-7.

3. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539-45.

4. Mantovani A et al. Cancer-related inflammation. Nature. 2008;454:436-44.

5. Piazuelo MB et al. Gastric cancer: an infectious disease. Infect Dis Clin North Am. 2010;24:853-69,vii.

6. Weitzman SA, Gordon LI. Inflammation and cancer: role of phagocyte-generated oxidants in carcinogenesis. Blood. 1990;76: 655-63.

7. Ohshima H. Genetic and epigenetic damage induced by reactive nitrogen species: implications in carcinogenesis. Toxicology Lett. 2003;140-141:99-104.

8. Brennecke J et al. bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila. Cell. 2003;113:25-36.

9. Chen CZ et al. MicroRNAs modulate hematopoietic lineage differentiation. Science. 2004;303:83-6.

10. Kirigin FF et al. Dynamic microRNA gene transcription and processing during T cell development. J Immunol. 2012;188:3257-67.

11. Carlsson J et al. A miRNA expression signature that separates between normal and malignant prostate tissues. Cancer Cell Int. 2011;11:14.

12. Carlsson J et al. Differences in microRNA expression during tumor development in the transition and peripheral zones of the prostate. BMC Cancer. 2013;13:362.

13. Ambs S et al. Genomic profiling of microRNA and messenger RNA reveals deregulated microRNA expression in prostate cancer. Cancer Res. 2008;68:6162-70.

14. Volinia S et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006;103:2257-61.

15. Porkka KP et al. MicroRNA expression profiling in prostate cancer. Cancer Res. 2007;67:6130-5.

16. Mattie MD et al. Optimized high-throughput microRNA expression profiling provides novel biomarker assessment of clinical prostate and breast cancer biopsies. Mol Cancer. 2006;5:24.

17. Wach S et al. MicroRNA profiles of prostate carcinoma detected by multiplatform microRNA screening. Int J Cancer. 2012;130:611-21.

18. O'Connell RM et al. microRNA regulation of inflammatory responses. Ann Rev Immunol. 2012;30:295-312.

19. Boldin MP et al. miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice. J Exp Med. 2011;208:1189-201.

20. Zhao JL et al. NF-kappaB dysregulation in microRNA-146a-deficient mice drives the development of myeloid malignancies. Proc Natl Acad Sci U S A. 2011;108:9184-9.

21. Taganov KD et al. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci U S A. 2006;103:12481-6.

22. Iyer A et al. MicroRNA-146a: a key regulator of astrocyte-mediated inflammatory response. PloS One. 2012;7:e44789.

23. Lin SL et al. Loss of mir-146a function in hormone-refractory prostate cancer. RNA. 2008;14:417-24.

24. Sheedy FJ et al. Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. Nat Immunol. 2010;11:141-7.

25. Prueitt RL et al. Expression of microRNAs and protein-coding genes associated with perineural invasion in prostate cancer. Prostate. 2008;68:1152-64.

26. Androulidaki A et al. The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs. Immunity. 2009;31:220-31.

27. O'Connell RM et al. Inositol phosphatase SHIP1 is a primary target of miR-155. Proc Natl Acad Sci U S A. 2009;106:7113-8.

28. O'Connell RM et al. MicroRNA-155 is induced during the macrophage inflammatory response. Proc Natl Acad Sci U S A. 2007;104:1604-9.

29. Tili E et al. Modulation of miR-155 and miR-125b levels following lipopolysaccharide/TNF-alpha stimulation and their possible roles in regulating the response to endotoxin shock. J Immunol. 2007;179:5082-9.

30. Tili E et al. Mutator activity induced by microRNA-155 (miR-155) links inflammation and cancer. Proc Natl Acad Sci U S A. 2011;108:4908-13.

31. Gironella M et al. Tumor protein 53-induced nuclear protein 1 expression is repressed by miR-155, and its restoration inhibits pancreatic tumor development. Proc Natl Acad Sci U S A. 2007;104:16170-5.

32. Iorio MV et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Res. 2005;65:7065-70.

33. Habbe N et al. MicroRNA miR-155 is a biomarker of early pancreatic neoplasia. Cancer Biol Ther. 2009;8:340-6.

34. Williams AE et al. Role of miRNA-146a in the regulation of the innate immune response and cancer. Biochem Soc Trans. 2008;36:1211-5.

35. Davidsson S et al. CD4 helper T cells, CD8 cytotoxic T cells, and FOXP3(+) regulatory T cells with respect to lethal prostate cancer. Mod Pathol. 2013;26:448-55.

36. Song MY et al. Genetic polymorphisms of miR-146a and miR-27a, H. pylori infection, and risk of gastric lesions in a Chinese population. PloS One 2013;8:e61250.

37. Xu B et al. A functional polymorphism in Pre-miR-146a gene is associated with prostate cancer risk and mature miR-146a expression in vivo. Prostate. 2010;70:467-72.

ROLE OF POSITRON EMISSION TOMOGRAPHY WITH FLUORODEOXYGLUCOSE IN PROSTATE CANCER

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ABSTRACT

Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT) has undergone explosive growth in clinical applications and has emerged as one of the most important imaging modalities in staging, restaging, detecting recurrence and/or metastasis, and monitoring therapeutic response, in most kinds of malignant diseases. However, to date, available experience with FDG PET/CT is limited in prostate cancer, mainly because prostate tumour is characterised by a slow glycolysis and low FDG avidity on PET imaging. Limited data suggested that FDG PET/CT might impact the clinical management of some prostate cancer in an adequate clinical setting, although this impact may be lower than that for other cancers. FDG PET/CT is useful for staging advanced prostate cancer with high Gleason score, detecting local recurrent or metastatic disease in some patients with biochemical failure, assessing treatment response, and providing prognostic information. More prospective clinical trials are underway to define the role of FDG PET/CT in prostate cancer, and more efforts will be made to develop novel radiotracers for PET imaging of prostate cancer.

Keywords: Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT), prostate cancer, glycolysis.

INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer in men, and continuously poses a major public health problem. During the last decade, there has been a significant advancement in the imaging of prostate cancer. Conventional imaging, which includes ultrasound, computed tomography (CT), and magnetic resonance (MR), is still used to detect organ-confined or metastatic disease for staging and determining prognosis, but a variety of emerging imaging techniques and probes have been accomplished. Today, the major goal for prostate cancer imaging is more accurate disease characterisation with anatomic, functional, and molecular imaging modalities. Since prostate cancer is clinically a heterogeneous disease characterised by biological behaviour that ranges between indolent and aggressive states, the selection of an imaging method should be based on the questions that need to be answered for a particular patient.

In recent years, positron emission tomography (PET) has undergone explosive growth in clinical applications and has emerged as one of the most important imaging modalities in staging, restaging, detecting recurrence and/or metastasis, and monitoring therapeutic response in most kinds of malignant diseases.[1,2] In PET, a trace amount of a radioactive compound is administered and the resultant images are obtained from three-dimensional spatial reconstructions. The intensity of the imaging signal is proportional to the amount of tracer, and therefore, is potentially semi-quantitative.[3] The major advantage of PET imaging over conventional imaging techniques is that PET provides information about changes of metabolism and function, which usually precede the anatomic abnormalities seen on conventional imaging. Combining molecular biology and *in vivo* imaging, PET enables the visualisation of cellular functions such as glucose metabolism, cell proliferation, cell membrane metabolism, or

receptor expression. In addition, the integrated PET/CT units allow correct co-registration and fused imaging of anatomical and functional data. CT imaging in an integrated PET/CT scanner significantly decreases false positive results and improves accuracy of the PET study.[4-6]

2-deoxy-2-(^{18}F)-fluoro-D-glucose (^{18}F-FDG) is the most commonly used radiotracer in PET imaging today. FDG is a non-physiological compound with a chemical structure very similar to that of naturally occurring glucose. Like glucose, FDG enters the cells through membrane glucose transporter proteins, which are commonly over-expressed in cancer cells.[7,8] The principle of FDG imaging is based on Warburg's observation, that the increased metabolic demands of rapidly dividing tumour cells require adenosine triphosphate generated by glycolysis. FDG is actively transported into cells through the membrane glucose transporters, and converted into FDG-6-phosphate by hexokinase. Since FDG-6-phosphate is not a substrate for the enzyme responsible for the next step in glycolysis, it is then trapped and accumulates in the cell in proportion to its glucose metabolic activity. Malignant cells exhibit increased FDG accumulation due to increased membrane transporters, increased intracellular hexokinase, and low glucose-6-phosphatase.

Unlike most malignancies, prostate tumour is characterised by a slow glycolysis and low FDG avidity on PET imaging. There is significant overlap between FDG uptake in prostate cancer and benign prostate hyperplasia.[9] An additional confounding problem is that FDG is normally excreted by the kidneys, and intense activity in the distended urinary bladder usually obscures the prostate, interfering with identification of pelvic lymph nodes.[10,11] Therefore, the exact clinical use of PET/CT in prostate cancer is not clear, and it is currently being explored. The following review will briefly discuss and illustrate the role of FDG PET/CT in prostate cancer.

PRIMARY DIAGNOSIS AND STAGING

The use of FDG PET in prostate cancer was first investigated in the mid-1990s focusing on the visualisation of primary tumours. It was shown that, unlike many other cancers, the FDG uptake in prostate cancer was similar to that of normal prostate tissue.[12,13] Although the overall clinical experience with FDG PET/CT in prostate cancer suffered from heterogeneity in published studies, with regard to the clinical phases of disease, there were relatively small numbers of patients, and variability and limitations in the validation criteria.[14] In general, FDG PET/CT might not be useful in the diagnosis or staging of clinically organ-confined disease due to low glycolysis of the tumour, or in the detection of locally recurrent disease because of the relatively similar FDG uptake by post-therapeutic changes or inflammation.[15,16] Since initial diagnosis of prostate cancer is relatively easy with serum prostate specific antigen (PSA) screening and transrectal biopsy, with or without ultrasound-guiding, FDG PET/CT is rarely used for the detection of primary prostate lesions.

However, some clinical studies also demonstrated that FDG PET/CT might be useful in certain clinical circumstances in prostate cancer. Sporadic cases showed increased FDG uptake in aggressive local prostate cancer. FDG uptake is higher in poorly differentiated primary tumour and higher PSA values than in tumours with more localised stage, and lower serum PSA values.[17] A recent investigation showed that FDG PET/CT has a sensitivity of 80% and a positive predictive value of 87% for detection of prostate cancer with Gleason score of 7 and greater in men who present with more than an intermediate-risk of prostate cancer based on elevated serum PSA level.[18] A case example in Figure 1 shows increased FDG uptake in a newly diagnosed primary prostate cancer lesion. The patient's serum PSA was 18.8 ng/ml and Gleason score was 7.

Information on lymph node status is of key importance when planning appropriate treatment for patients with newly diagnosed prostate cancer. Although conventional imaging modalities such as CT and MRI are often used to detect nodal disease, some observations suggested that FDG PET/CT is more sensitive than anatomic imaging in detection of nodal metastasis. Heicappel et al.[19] investigated the use of FDG PET in determining pelvic lymph node metastases and found that FDG PET was positive in four of six patients with histologically-confirmed lymph node spread, which was superior to the CT imaging.

The most common organ for distant metastasis in prostate cancer is bone. FDG PET/CT is variable in the detection of bone metastasis and it was reported to be less sensitive than conventional bone scintigraphy.[20,21] But one of the

significant advantages of FDG PET/CT over bone scintigraphy, is that FDG PET can discriminate active osseous disease from quiescent lesions on scintigraphy. In other words, FDG PET is more specific than bone scintigraphy to detect active disease.[20] FDG predominately detects those lesions with increased osteoclastic activity, which is likely to be more aggressive, indicating a poorer prognosis. Oyama et al.[22] reported a decrease in FDG uptake in prostate cancer and metastatic lesions after endocrine therapy, suggesting that glucose use by tumours was suppressed by androgen ablation.

BIOCHEMICAL FAILURE AND RESTAGING

Post-therapeutic biochemical failure in prostate cancer represents a diagnostic dilemma, and poses a great challenge to urologists and oncologists. By definition, biochemical failure indicates PSA relapse, but without evidence of disease with standard imaging. FDG PET/CT has shown a promising role in detection of local recurrence or metastatic disease. In a study of 24 patients with rising PSA after treatment of localised prostate cancer, both CT and FDG PET/CT were obtained prior to pelvic lymph node dissection.[23] The CT was negative in all cases, but

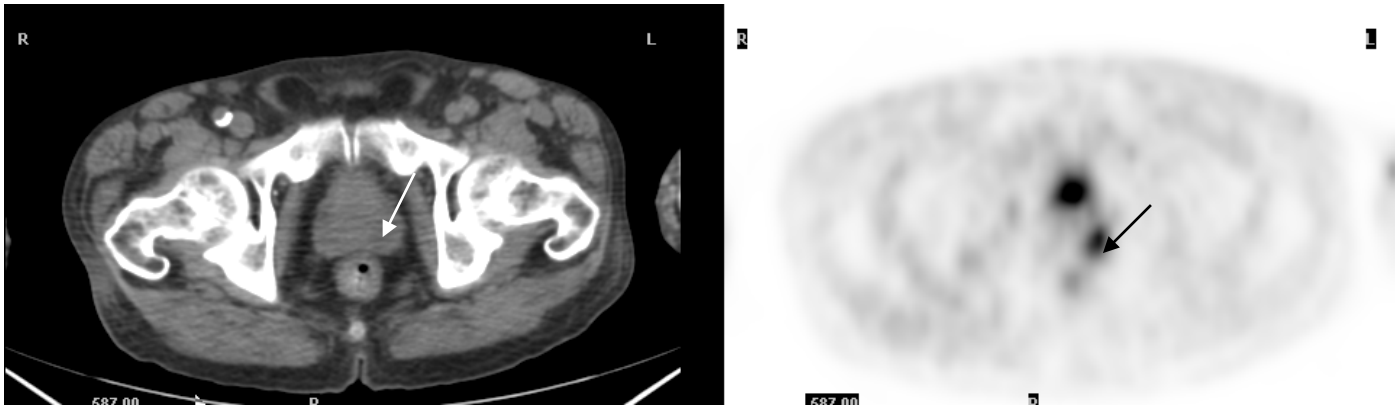

Figure 1. A 63-year-old patient had newly diagnosed prostate cancer with serum PSA 18.8 ng/ml and Gleason score 7.
FDG PET/CT images show a FDG avid low density lesion in the left sided periphery of the prostate (arrows).

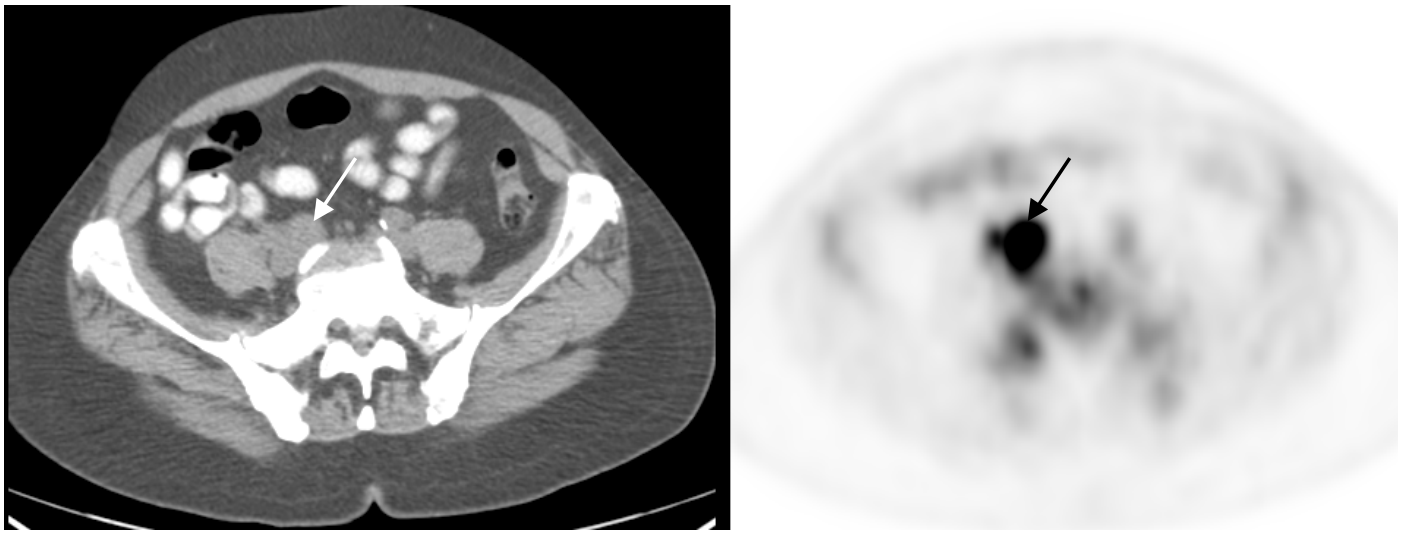

Figure 2. A 62-year-old patient with rising PSA level 2 years after radiation and hormonal therapy.
A whole-body FDG PET/CT showed a highly FDG avid right iliac node, seen on the axial images of the CT (the left) and PET (the right, arrows). Surgical pathology from lymphadenectomy confirmed metastasis from prostate cancer.

FDG PET/CT detected 75% histopathologically-proven metastases. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG PET/CT in detecting metastatic pelvic lymph nodes were 75%, 100%, 83%, 100%, and 68%, respectively. In another retrospective study of 91 patients with PSA, relapse after prostatectomy and validation of tumour presence by biopsy or clinical and imaging follow-up, FDG PET/CT detected local or systemic disease in 31% of patients.[24] The study also demonstrated that mean PSA level was higher in patients with positive PET findings than in those with negative PET. FDG PET may be particularly useful in the restaging of advanced prostate cancer in patients who have a rising PSA level despite treatment.[25] FDG PET is also advantageous over 111In-capromab pendetide scintigraphy in the detection of metastatic disease in patients with high PSA levels or high PSA velocity.[26]

Three case examples are shown in the Figures 2-4, demonstrating FDG-avid metastatic lesions in the lymph node, adrenal gland, and bone.

TREATMENT RESPONSE ASSESSMENT AND PROGNOSTICATION

FDG PET/CT was also incorporated into the evaluation of treatment response. Oyama et al.[22] investigated 10 patients with histologically-proven prostate cancer before and after endocrine treatment. It was shown that FDG accumulation within both prostate and metastatic lesions was reduced in all patients within 1-5 months after commencing therapy. Series FDG PET has also been studied to predict outcome of chemotherapy in castrate-resistant metastatic disease, which demonstrated that FDG PET correctly identified the clinical status in 91% of patients at 4 weeks and 94% of patients at 12

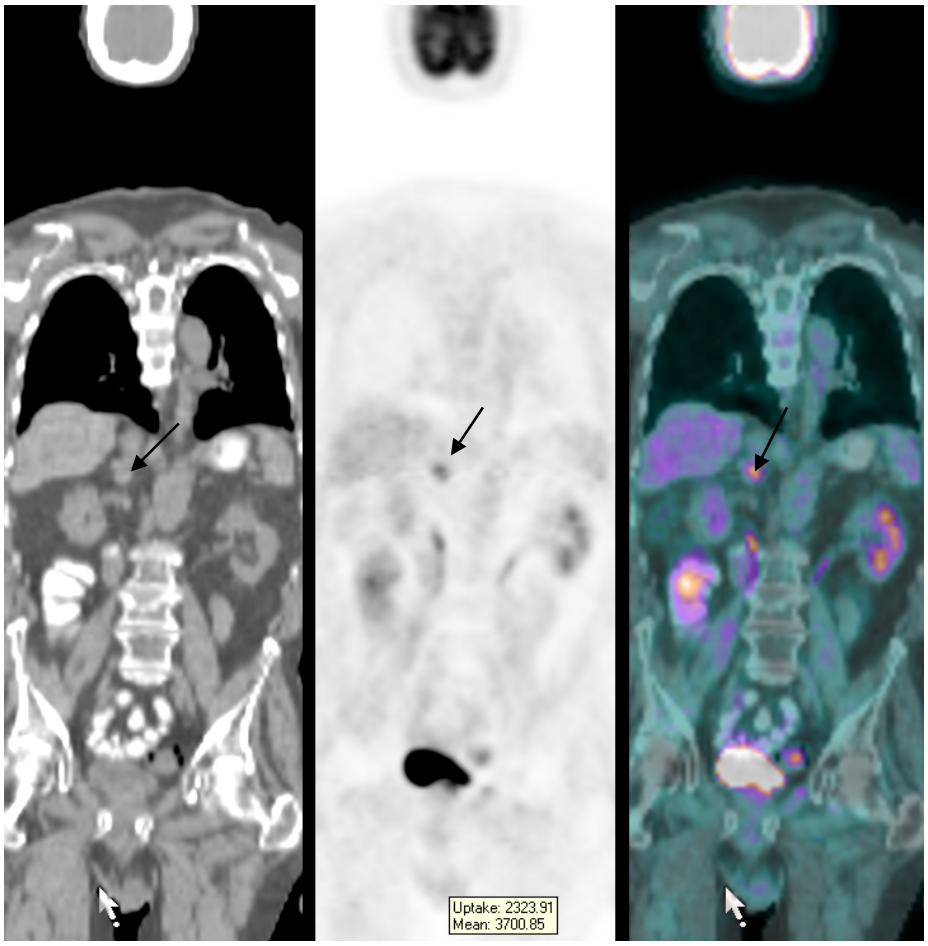

Figure 3. An 83-year-old patient with rising PSA level 3 years post-hormonal therapy for prostate cancer. A whole-body FDG PET/CT showed a right adrenal nodule with intense uptake, as arrows indicated on the coronal imaging of the CT (the left), PET (the middle) and fused imaging (the right). The follow-up CT suggested right adrenal metastasis.

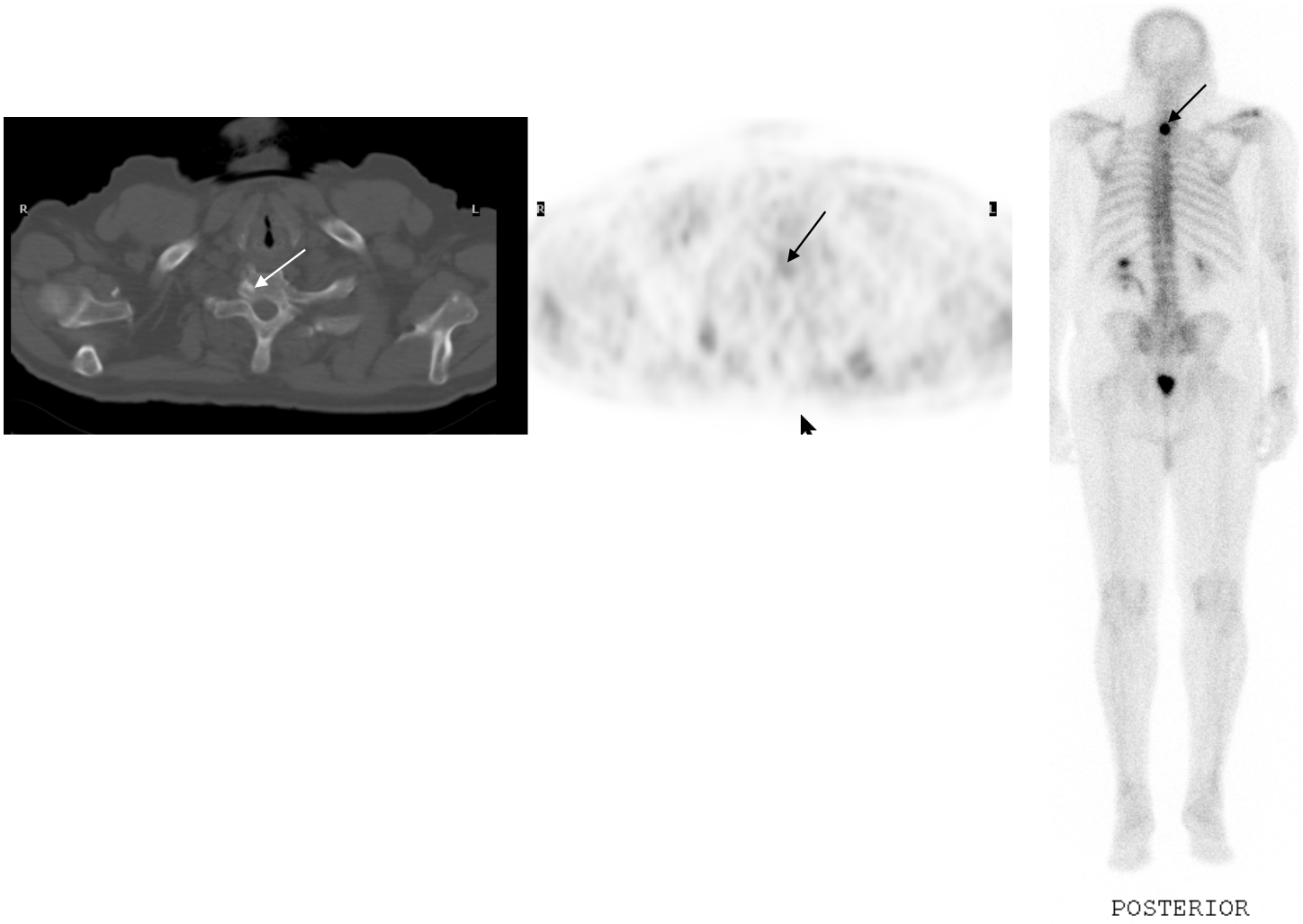

Figure 4. A 70-year-old patient with rising PSA level 5 years after prostatectomy.
A whole-body FDG PET/CT showed a small sclerotic lesion with mild FDG uptake in the right-sided T1 vertebral body (arrows). Bone scintigraphy 2 months later demonstrated intense focal uptake in the same region, consistent with metastasis.

weeks, including combination of PSA, bone scintigraphy and anatomic imaging.[27] FDG PET might have the potential as a surrogate marker of response to chemotherapy in castrate-resistant disease.

The level and extent of FDG accumulation in primary prostate and metastatic lesions may provide information on prognosis. Oyama et al.[28] reported that patients with high FDG avid primary prostate tumours had a poorer prognosis compared to those with low uptake of the tumours. An increase of over 33% in the average maximum FDG uptake was reported to be able to categorise castrate-sensitive metastatic prostate cancer patients treated with antimicrotubule chemotherapy into progressors or nonprogressors.[27] Recently, Jadvar et al.[29] reported prognostic role of FDG PET/CT parameters in castrate-resistant prostate cancer. 87 men with castrate-resistant metastatic prostate cancer underwent FDG PET/CT and were followed prospectively for overall survival. PET parameters included the maximum standardised uptake value (SUVmax) of all metabolically active lesions, after subtraction of patient-specific background-liver average SUV. The result showed that the sum of SUV_{max} derived from FDG PET/CT contributes independent prognostic information on overall survival in men with castrate-resistant metastatic prostate cancer. However, larger prospective studies are further required to substantiate these preliminary findings.

NOVEL PET TRACERS FOR PROSTATE CANCER

In recent years, much effort has been made to develop novel radiotracers for PET imaging of prostate cancer, such as tracers that can identify cell membrane turnover, protein synthesis, DNA synthesis, and testosterone metabolism within the prostate.[30-33] Among them, C11/F18-choline has been studied most extensively. Choline is a substrate for phospholipid synthesis in cell membranes, transmembrane signaling, lipid and cholesterol transport, and metabolism. There is a growing body of literature supporting the utility of choline in early-stage prostate cancer.[34] Acetate is a molecule absorbed by cells and converted into acetyl-CoA. C11-acetate has been investigated for intra-prostatic primary tumour detection and staging as well as restaging.[35] F18-fluoro-5α-dihydrotestosterone (F18-FDHT) targets the androgen receptor and may be particularly useful in the assessment of the pharmacodynamics of the androgen signaling pathway.[36] F18-sodium fluoride (NaF) PET/CT is more valuable to detect osseous metastasis, superior to FDG PET/CT.[37]

CONCLUSION

FDG PET/CT might impact the clinical management of some prostate cancer in adequate clinical settings, although this impact may be lower than that for other cancers. FDG PET/CT is useful for staging advanced prostate cancer with high Gleason score, detecting local recurrent or metastatic disease in some patients with biochemical failure, assessing treatment response, and providing prognostic information. However, to date, available experience with FDG PET/CT is limited, and more prospective clinical trials are underway to define the role of FDG PET/CT in prostate cancer. In addition, much effort was made to develop novel radiotracers for PET imaging of prostate cancer in recent years, such as tracers that can identify cell membrane turnover, protein synthesis, DNA synthesis, and testosterone metabolism within the prostate.

REFERENCES

1. Fletcher JW et al. Recommendations on the use of 18F- FDG PET in oncology. J Nucl Med. 2008;49:480-508.

2. Rohren EM et al. Clinical applications of PET in oncology. Radiology. 2004;231:305-32.

3. Kapoor V et al. An introduction to PET/CT imaging. RadioGraphics. 2004;24:523-43.

4. Antoch G et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. J Clin Oncol. 2004;22:4357-68.

5. Pelosi E et al. Value of integrated PET/CT for lesion localisation in cancer patients: a comparative study. Eur J Nucl Med Mol Imaging. 2004;31:932-9.

6. Reinartz P et al. Side-by-side reading of PET and CT scans in oncology: which patients might profit from integrated PET/CT? Eur J Nucl Med Mol Imaging. 2004;31:1456-61.

7. Delbeke D, Martin WH. Positron emission tomography imaging in oncology. Radiol. Clin North Am. 2001;39:883-917.

8. Liu Y et al. Physiology and pathophysiology of incidental findings detected on FDG-PET scintigraphy. Semin Nucl Med. 2010;40:294-315.

9. Salminen E et al. Investigations with FDG PET scanning in prostate cancer show limited value for clinical practice. Acta Oncol. 2002;41:425-9.

10. Ravizzini G et al. New horizons in prostate cancer imaging. Eur J Radiol. 2009;70:212-26.

11. Lawrentschuk N et al. Positron emission tomography and molecular imaging of the prostate: an update. BJU International. 2006;97:923-31.

12. Effert PJ et al. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18fluorine-labeled deoxyglucose. J Urol. 1996;155:994-8.

13. Hofer C et al. Fluorine-18-fluorodeoxyglucose positron emission tomography is useless for the detection of local recurrence after radical prostatectomy. Eur Urol. 1999;36:31-5.

14. Jadvar H. Prostate cancer: PET with 18F-FDG, 18F- or 11C-Acetate, and 18F- or 11C-Choline. J Nucl Med. 2011;52:81-9.

15. Liu IJ et al. Fluorodeoxyglucose positron emission tomography studies in diagnosis and staging of clinically organ-confined prostate cancer. Urology 2001;57:108-11.

16. Castellucci P, Jadvar H. PET/CT in prostate cancer: non-choline radiopharmaceuticals. Q J Nucl Med Mol Imaging. 2012;56:367-74.

17. Oyama N et al. The increased accumulation of 18F fluorodeoxyglucose in untreated prostate cancer. Jpn J Clin Oncol. 1999;29:623-9.

18. Minamimoto R et al. The potential of FDG PET/CT for detecting prostate cancer in patients with an elvetaed serum PSA level. Ann Nucl Med. 2011;25:21-7.

19. Heicappel R et al. Staging of pelvic lymph nodes in neoplasms of the bladder and prostate by positron emission tomography with 2-[(18)F]-2-deoxy-D-glucose. Eur Urol. 1999;36:582-7.

20. Morris MJ et al. Fluorinated deoxyglucose positron emission tomography imaging in progressive metastatic prostate cancer. Urology. 2002;59:913-8.

21. Fogelman I et al. Positron emission tomography and bone metastases. Semin Nucl Med. 2005;35:135-42.

22. Oyama N et al. FDG PET for evaluating the change of glucose metabolism in prostate cancer after androgen ablation. Nucl Med Commun. 2001;22:963-9.

23. Chang CH et al. Detecting metastatic pelvic lymph nodes by 18F-2-deoxyglucose positron emission tomography in patients with prostate-specific antigen relapse after treatment for localized prostate cancer. Urol Int.

2003;70:311-5.

24. Schoder H et al. 2-[18F]fluororo-2-deoxyglucose positron emission tomography for detection of disease in patients with prostatic-specific antigen relapse after radical prostatectomy. Clin Cancer Res. 2005;11:4761-9.

25. Sung J et al. Fluorodeoxyglucose positron emission tomography studies in the diagnosis and staging of clinically advanced prostate cancer. BJU Int. 2003:92:24-7.

26. Seltzer MA et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. J Urol. 1999;162:1322-8.

27. Morris MJ et al. Fluorodeoxyglucose positron emission tomography as an outcome measure for castrate metastatic prostate cancer treated with antimicrotubule chemotherapy. Clin Cancer Res. 2005;11:3210-6.

28. Oyama N et al. Prognostic value of 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography imaging for patients with prostate cancer. Mol Imaging Biol. 2002;4:99-104.

29. Jadvar H et al. Baseline F18-FDG PET/CT parameters as imaging biomarkers of overall survival in castrate-resistant metastatic prostate cancer. J Nucl Med. 2013;54:1195-201.

30. Shiiba M et al. Evaluation of primary prostate cancer using 11C-methionine-PET/CT and 18F-FDG-PET/CT. Ann Nucl Med. 2012;26:146.

31. Jadvar H. Prostate cancer. Methods Mol Biol. 2011;727:265-90.

32. Bouchelouche K et al. PET/CT imaging and radioimmunotherapy of prostate cancer. Semin Nucl Med. 2011;41:29-44.

33. Lee ST et al. PET in prostate and bladder tumors. Semin Nucl Med. 2012;42:231-46.

34. Fox JJ et al. Molecular imaging of prostate cancer. Curr Opin Urol. 2012;22:320-27.

35. Wachter S et al. C11-acetate positron emission tomography imaging and imaging fusion with computed tomography and magnetic resonance imaging in patients with recurrent prostate cancer. J Clin Oncol. 2006;24:2513-9.

36. Beattie BJ et al. Pharmacokinetic assessment of the uptake of 16beta-18F-fluoro-5alpha-dihydrotestosterone (FDHT) in prostate tumors as measured by PET. J Nucl Med. 2010;51:183-92.

37. Jadvar H et al. Prospective evaluation of F18-NaF and F18-FDG PET/CT in detection of occult metastatic disease in biochemical recurrence of prostate cancer. Clin Nucl Med. 2012;37:637-43.

GENOMIC TESTING IN INTERNATIONAL GUIDELINES

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ABSTRACT

Human breast cancer was solely classified based on clinical and immunohistochemical (IHC) findings in the past. A growing body of evidence suggests that these categorisations are rendered more precisely by intrinsic subtyping with the aim of an introduction of personalised medicine. Especially in breast cancer with the uncertain potential of disease spread, such as T1-2, Grade 2 and oestrogen receptor-positive (ER+ve) tumours, the value of chemotherapy applied to every patient has been questioned and the need for additional information on the tumour´s specific risk of recurrence is overt. It is estimated that the average risk for recurrence is 15% at 10 years in hormone-receptor-positive breast cancer. Thus, a relatively small proportion of these patients would need chemotherapy, and the main task is to stratify which patients of this cohort are at high-risk and will benefit from cytotoxic agents. Ki67, as a proliferation marker classifying high-risk tumours, has been demonstrated as a continuous marker, but not as a clear cut risk-defining instrument in recent publications. Thus, the difficulties are perceived especially at the threshold of the low to high-risk area of this marker. Reproducibility of Ki67 is to some extent uncertain considering there is inter and intra-institutional variability of up to 30% of the results. Several multigene arrays, such as MammaPrint®, Oncotype DX®, Endopredict®, and PAM50 have demonstrated clinical utility and experienced validation. The aim of this review is the description of the implementation of genomic testing in international guidelines (North American and European), with regard to incorporation of multigene arrays into the decision-making process in different clinical settings (including tumour size and IHC status). Data cut-off was 1st October, 2013. It seems that North America and some European countries have initiated a shift towards a personalised medicine with multigene arrays based on RT-PCR or microarrays.

Keywords: Breast cancer, gene array, guidelines, Oncotype DX®, MammaPrint®, Rotterdam signature-prognosis, prediction-chemotherapy response.

INTRODUCTION

After a century of predicting the prognosis of early human breast cancer solely on clinical and immunohistochemical findings, Sorlie et al.[1] initiated at the transition of the millennium a change of paradigm in deciphering breast cancer prognosis with their milestone paper on intrinsic subtypes. Furthermore, within their defined two groups of oestrogen receptor-positive (ER+ve) breast cancers (Luminal A and B), a large variety of risk population is allocated. These two subtypes have been subject to repeated attempts of differentiation and approximation immunohistochemically by grading (St. Gallen, 2009)[2] or Ki67 (St. Gallen, 2011)[3] with a shift of from ≥15% to ≥20% in the threshold from a low to high Ki67 from 2011 to 2013. Denkert et al.[4] however, published in their current analysis of pre-therapeutical core biopsies of 1,166 early breast cancer patients that Ki67 is a continuous marker with regard to the clinical endpoints of disease-free survival (DFS) in a range of 6-46% and overall survival (OS) of 4-58%. Thus, the cut-off range defined by the

latest St. Gallen consensus lies in the midst of a continuous field of risk points. Absolute borders to differentiate Luminal A from Luminal B on the basis of an immunohistochemical approximation may be defined for practical reasons, but not strictly on biologically founded grounds.

Given this obscurity in determining the actual risk profile of hormone receptor-positive (HR+ve) breast cancer, and also other breast cancer subtypes, we set out to analyse whether National North American (American Society of Clinical Oncology [ASCO] guidelines)[5] and European guidelines provide recommendations for physicians in this zone of ambiguity of clinical management. The commercially available genomic tests are MammaPrint® (prognostic: lymph node [N]0-1), Oncotype DX® (prognostic and predictive: N0-1, ER+ve), Endopredict® (prognostic, postmenopausal, N0-1, ER+ve, HER2-ve), and PAM50 (prognostic subtype classifier, N0-1) (Table 1).

Access to Genomic Testing

After numerous studies on genomic testing, also combined with other endocrine and chemotherapy regimens,[6] genomic tests have been entered into clinical practice as Abu-Khalf et al.[7] published

Table 1. Genomic tests and their evaluation in the German AGO-guidelines (Version 2013.1)[13]

	MammaPrint®	Oncotype DX®	Endopredict®	PAM50
Provider	Agendia	Genomic Health	Sividon	NanoString
Type of assay	70-gene assay	21-gene RS	11-gene assay	50-gene assay
Type of tissue	Fresh frozen	FFPE	FFPE	FFPE
Technique	DNA microarrays	qRT-PCR	qRT-PCR	qRT-PCR
Central lab	yes	yes	no	yes
Indication and population studied	Prognostic N0-1	Prognostic N0-1 ER+ve	Prognostic postmenopausal N0-1 ER+ve HER2-ve	Prognostic subtype classifier N0-1
Analytical validation	no	yes	yes	no
Clinical validation	yes	yes	yes	yes
Clinical utility	no	yes	yes	no
Prospective-retrospective evidence		NSABP B-14 NSABP B-20 ECOG 9127 SWOG 8814 ATAC	ABCSG 6 ABCSG 8	MA.12 MA.5
Prospective evidence (pending)	MINDACT	TAILORx RxPONDER		

RS: Recurrence Score; FFPE: formalin-fixed paraffin-embedded; qRT-PCR: quantitative reverse transcription polymerase chain reaction; ER: oestrogen; HER2: human epidermal growth factor receptor 2; N: node; NSABP: National Surgical Adjvant Breast and Bowel Project; ECOG: Eastern Cooperative Oncology Group; SWOG: Southwest Oncology Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; ABCSG: Austrian Breast and Colorectal Cancer Study Group; MA: mammary.

most recently. The authors asserted that today 30%, 13% and 1% of Stage I, II and III ER+ve breast cancers are tested and that among those who are tested, genomic testing changed the recommendation in approximately 25-30% of cases. Almost all cost-effectiveness studies, the authors concluded, demonstrated a positive result when the tests are used under current guidelines. However, the main reason for not having access to genomic testing is not driven by the personal economic situation, but the fact that the treating physician did not offer it (80%), as Defrank et al.[8] analysed. Defrank also found, by interviewing (n=123) patients eligible for the 21-gene array test, that those having received such a test described their decision-making style with regard to chemotherapy as active (75%), whereas only a minority who received the test described their style as passive (12%) ($p<0.01$).

Given the cost-effectiveness and the empowerment of patients for a more active role in decision-making, pondering the pro or cons of chemotherapy in early breast cancer, and the obstacle of missing offers of genomic testing by physicians, we scrutinised whether more recent and precise national guidelines of the genomic testing of North America and Europe exist.

METHODS

Published North American and European guidelines were analysed with regard to implementation of directives on genomic testing in the management of early breast cancer. Data cut-off was 1st October, 2013.

RESULTS

ASCO Guidelines Update 2007

As early as in 2007, the ASCO guidelines were the first international guidelines to be published by Harris et al.,[5] incorporating multigene arrays into their panel of 'Recommendation on the Use of Tumour Markers in Breast Cancer.' These guidelines commented on four multigene arrays in node-negative (N-ve), ER+ve breast cancer: Oncotype DX® assay (21-gene array), Amsterdam signature (MammaPrint®, 70-gene array), Rotterdam signature (76-gene array), and the Breast Cancer Gene Expression ratio. Out of these, Oncotype DX® and MammaPrint® attracted the main focus of the ASCO panel, however for 'newly diagnosed patients with N-ve, ER+ve breast cancer,' only the Oncotype DX® assay was approved 'to be used to predict the risk of recurrence in patients treated with tamoxifen and to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy.' In addition, patients with high Oncotype DX® Recurrence Scores (RS) were recognised 'to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from Tamoxifen.'

However, the ASCO panel considered that there was 'insufficient data at that time to comment on whether these conclusions generalise to hormonal therapies other than Tamoxifen, or whether this assay applies to other chemotherapy regimens.' The precise clinical utility and appropriate application for other multi-parameter assays, such as the MammaPrint® assay, the 'Rotterdam Signature,' and the Breast Cancer Gene Expression Ratio were classified as being 'still under investigation,' which meant no positive consideration so far in the ASCO guidelines.

NCCN Guidelines 3.2013

National Comprehensive Cancer Network (NCCN) has more precisely updated its recent guidelines - Version 3.2013[9] - on the use of genomic testing (Figure 1). In HR+ve, HER2-HER2-ve early breast cancer of Stages pT1-3 N0 or $N1_{mic}$ (<2 mm), the guidelines recommend for tumours of >5 mm to consider a 21-gene RT-PCR array (Oncotype DX®). Depending on the RS, the NCCN stratifies the clinical management pathway as follows: RS <18 (low RS) recommending adjuvant endocrine therapy only, RS 18-30 (intermediate RS) suggesting potentially (+/-) additional adjuvant chemotherapy and >31 (high RS) definitely recommending additional chemotherapy. In N+ve disease (one or two ipsilateral lymph node metastasis >2 mm) adjuvant chemotherapy is unequivocally recommended.

St. Gallen 2013 International Expert Consensus

Guidelines of the St. Gallen 2013 International Expert Consensus on the Primary Therapy of Early Breast Cancer declared that intrinsic subtypes should determine whether chemotherapy should be applied but not which type of chemotherapy. In ER+ve, HER2-ve, N-ve breast cancer a slim, but definite majority of experts of the panel voted in favour of requesting a

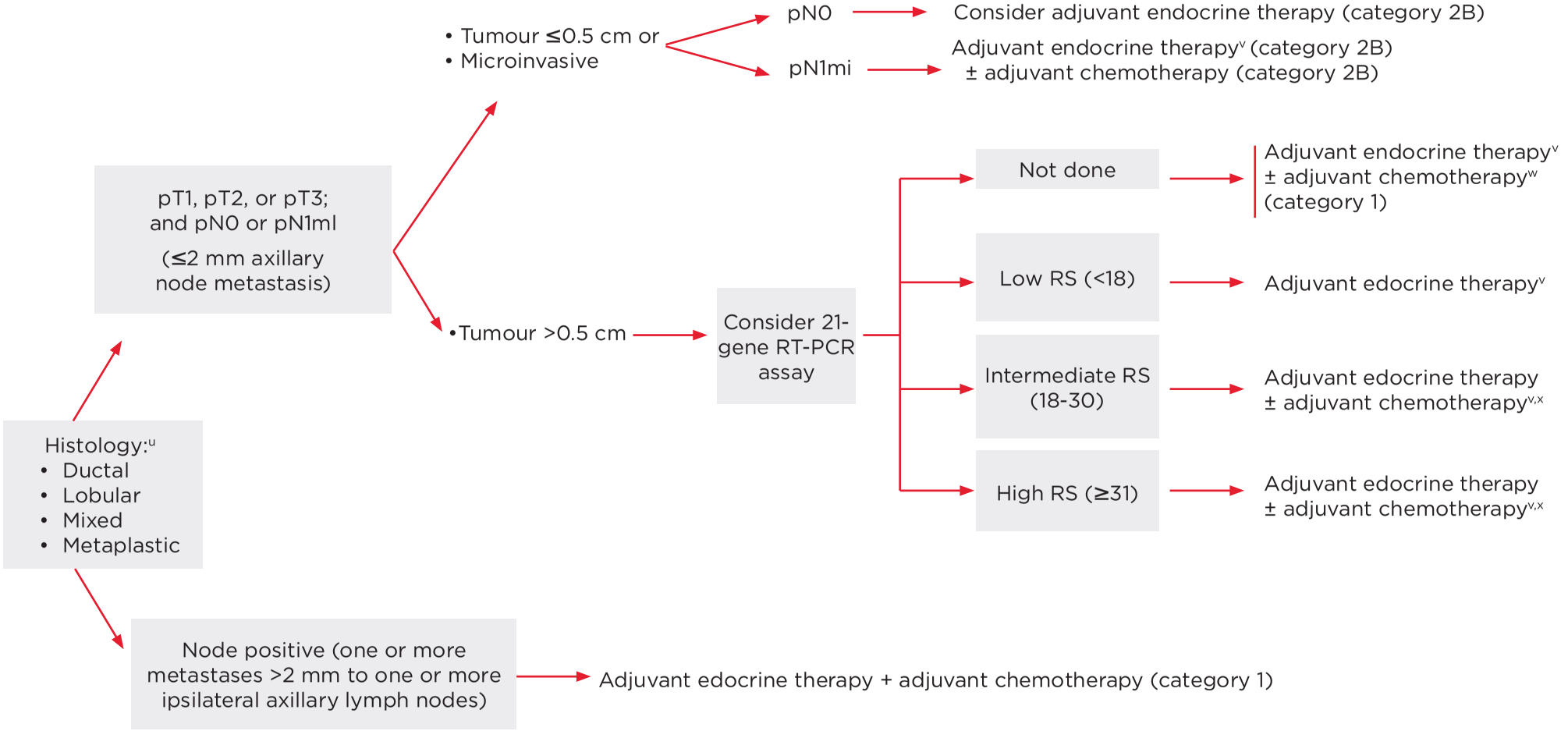

Figure 1. NCCN-guidelines 3.2013 (adapted).

[u] Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[v] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. Early evident suggests similar benefits from ovarian suppression (ie, Luteinising hormone-releasing hormone) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

[w] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[x] There are limited data to make chemotherapy recommendations for those >70 yr old. Treatment should be individualised with consideration of comorbid conditions.

multigene array. The 21-gene RS was judged to be predictive of chemotherapy responsiveness by the majority of panel members; however this was not the case for PAM50 or the EPClin. For the 70-gene signature it was a split vote of 25% in favour, and 25% in opposition, and the rest of the panel voted for abstention.

At tumour size ≤1 cm – contrary to the NCCN guidelines 3.2013 which also cover tumour sizes of 5-10 mm as eligible for genomic testing – request for a gene array was deemed unnecessary by the St. Gallen panel members. On the other end, with tumour size >5 cm, inflammatory breast cancer, cases of >4 positive lymph nodes or very low ER positivity (e.g. 5%) required chemotherapy without use of gene arrays as decision assistance due to the St. Gallen panel 2013. This however, was felt to be different for selected patients with one to three positive lymph nodes and patients aged <35 years.[10]

ESMO Guidelines 2013

The most recent European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up of primary breast cancer,[11] which are also endorsed by the Japanese Society of Medical Oncology (JSMO) names two out of four commercially available genomic tests as suitable for treatment decision-making in 'some cases, such as Grade 2 ER+ve HER2-ve and N-ve breast cancer, in conjunction with all clinic-pathological factors' – these are again the 21-gene array and 70-gene array. The ESMO recommendation is irrespective of the actual size of the tumour; however the ESMO guidelines point at the awaited prospective clinical trials MINDACT, TAILORx and RxPonder to define the optimal and accurate use of these tests in the clinical setting.

UK NICE Guidelines 2013

The National Institute for Health and Care Excellence (NICE) in the United Kingdom has released its final recommendation on genomic testing in early breast cancer[12] after a long process of evaluation of the 21-gene-array, 70-gene array, IHC4 and Mammostrat. The decision, published in early September 2013, declared 21-gene array is 'recommended as an option for guiding adjuvant chemotherapy decisions for people with ER+ve, N-ve, and HER2-ve early breast cancer if:

• the person is assessed as being at intermediate-risk* and

• information on the biological features of the cancer provided by Oncotype DX® is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy and

• the manufacturer provides Oncotype DX® to National Health Service (NHS) organisations according to the confidential arrangement agreed with NICE.'

(*'Intermediate-Risk' of distant recurrence was defined as a Nottingham Prognostic Index [NPI] score above 3.4. Also other decision-making tools or protocols currently used in the NHS may also be used to identify people at intermediate-risk according to NICE Guidelines.)

Other genomic tests investigated by NICE, such as MammaPrint®, IHC4 and Mammostrat, were only 'recommended for use in research in people with ER+ve, N-ve and HER2-ve early breast cancer, to collect evidence about potentially important clinical outcomes and to determine the ability of the tests to predict the benefit of chemotherapy (...). The tests are not recommended for general use in these people because of uncertainty about their overall clinical benefit and consequently their cost-effectiveness.'

Germany

In Germany, the AGO (Working Group of Gynecological Oncology) within the German Society of Obstetrics and Gynecology and German Cancer Society, has updated its guidelines in March 2013.[13] It defined as prognostic factors in early breast cancer two validated multigene arrays in HR+ve subset of breast cancer: Oncotype DX® and EndoPredict®. The AGO ascertained the evidence as Level of Evidence (LoE) 2009 IB, Group B recommendation, and concluded that these multigene arrays may be an option (+/-). Other gene arrays like Mammostrat and PAM50 also received the same categorisation, however PAM50 and MammaPrint® in N0-1 only with LoE 2009 IIB-evidence. For response prediction in neoadjuvant chemotherapy PAM50 and MammaPrint® had a LoE 2009 of IIIC, with an optional recommendation from the AGO (+/-). For prediction of the benefit of adjuvant chemotherapy only Oncotype DX® had a LoE 2009

IB and is mentioned as the only multigene array (recommendation grade (+/-)).

The German interdisciplinary S3-guideline for diagnosis, therapy and follow-up of breast cancer Version 3.0 was issued in July 2012, and – contrary to the AGO-guidelines – did not consider gene arrays (PCR-based or microarray-based) as clinically sufficient validation to be recommended.[14]

The Netherlands

The Dutch Guidelines for Breast Cancer, Version 2.0, 2012[15] suggest three gene arrays to be eventually considered in different clinical settings: MammaPrint®, Rotterdam Signature, and Oncotype DX®, for which they state: 'It has been demonstrated for a number of gene expression profiles in retrospective studies that they are better at distinguishing subgroups with a favourable or unfavourable prognosis than traditional risk estimations.'

The Dutch guidelines attribute LoE II to these gene arrays to determine the prognosis.

For prediction of chemotherapy response, the Dutch guidelines state that the predictive value of MammaPrint® for the effect of adjuvant chemotherapy has not yet been proven, whereas this is acknowledged for Oncotype DX® according to the NSABP B20 trial. However the Dutch guidelines add that the predictive value of the gene profile has not been prospectively researched with newer therapeutic modalities such as aromatase inhibitors, other chemotherapy agents or trastuzumab.

Other European Countries

No specific guidelines were retrievable from other countries´ official national boards.

CONCLUSION

North America and some European countries have initiated a shift from mere histologically and clinically-driven risk stratification and chemotherapy response prediction towards a personalised medicine based on multigene arrays by RT-PCT or microarrays. LoE attributed to these arrays is varying due to the approach used in classifying the underlying studies. Most guidelines see a preference for Onctoype DX and MammaPrint® as validated multigene arrays (Table 2). Expert panels like St. Gallen International Expert Consensus guidelines have a preference for Oncotype DX®, especially with regard to chemotherapy response prediction. Prospective trials especially concerning these two multigene arrays are eagerly awaited, and outcomes will be presented in the near future, like trial results of the RxPONDER, TAILORx AND MINDACT trials. Refunding of multigene arrays by national health systems is implemented partly in some European countries, such as the UK and to some extent in Germany as well. The genomic era has not yet arrived, but the dawn has already begun in some parts of the world.

Table 2: Summary – genomic tests in international guidelines.

	Oncotype DX®	MammaPrint®	Rotterdam Score	PAM50	Mammostrat	IHC 4	EPClin
ASCO 2007[5]	YES	-	-	-	-	-	-
NCCN 2013[9]	YES	-	-	-	-	-	-
St. Gallen 2013[10]	YES	+/-	-	-	-	-	-
ESMO 2013[11]	YES	YES	-	-	-	-	-
UK(NICE) 2013[12]	YES	-	-	-	-	-	-
Germany (AGO) 2013[13]	YES	-	-	-	-	-	YES *
Netherlands 2012[15]	YES	YES	YES	-	-	-	-

(* EPClin restricted to postmenopausal women and only for prognosis, not for prediction of chemotherapy response)

REFERENCES

1. Sorlie T. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869-74.

2. Goldhirsch A. Threshold for therapies: highlights of the St Gallen international expert consensus on the primary therapy of early breast 2009. Ann Oncol. 2009;20(8):1319-29.

3. Goldhirsch A. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol. 2011;22(8):1736-47.

4. Denkert C et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant Gepar Trio trial. Ann Oncol. 2013;24(11):2786-93.

5. Harris L et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25(33):5287-312.

6. Albain K. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010;11(1):55-65.

7. Abu-Khalf M et al. Influence of genomics on adjuvant treatments for pre-invasive and invasive breast cancer. Breast. 2013;22 Suppl 2:S83-7.

8. Defrank JT et al. Who gets genomic testing for breast cancer recurrence risk? Public Health Genomics. 2013;16(5):215-22.

9. NCCN Clinical Practice Guidelines guidelines in Oncology (NCCN guidelines). Breast Cancer Version 3.2013.

10. Goldhirsch A. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2013. Ann Oncol. 2013;24(9):2206-23.

11. Senkus E. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi7-vi23.

12. National Institute for Health and Care Excellence; NICE diagnostic guidance 10. Gene expression profiling an expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management. Issued: September 2013. www.nice.org.uk/dg10.

13. AGO, German Society of Obstetrics and Gynaecology, German Cancer Society, guidelines March 2013. AGO recommendations for diagnosis and treatment of patients with primary and metastatic breast cancer. Guidelines Breast Version 2013.1D.

14. Kreienberg R et al. German Cancer Society (DKG). Interdisciplinary S3-guideline diagnosis, therapy and follow-up of breast cancer. Issued: July 2012.

15. The Dutch Guidelines. Breast Cancer. Version 2.0. 2012.

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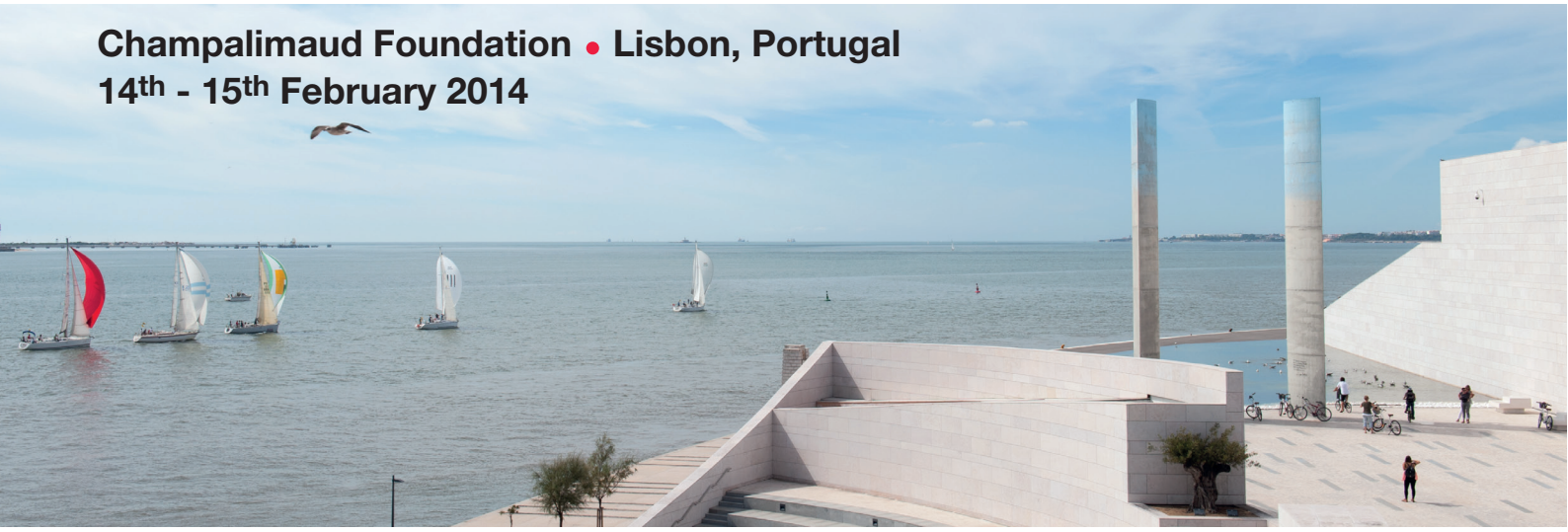

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Programme

Complete Response - triumph or tragedy?
Opening lecture

Session 1 The impact of the Complete Response (CR) Concept around the world. Where have we all got to so far?
Session 2 Which rectal cancer patients should be candidates for a Watch & Wait (W&W) strategy?
Session 3 What is the best treatment to increase response rates?
Session 4 How should we evaluate treatment response?
Session 5 How to manage the complete responders?
Session 6 How to manage the incomplete responders and regrowths?
Session 7 Future perspectives in the conservative treatment of rectal cancer?
Closing lecture The changing morphology of regression & regrowth. Molecular biology. What may enable us to predict the Complete Response?

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METASTASIS OF DUCTAL BREAST CARCINOMA TO THE VAGINA: A CASE REPORT

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ABSTRACT

Primary cancers of the vagina are rare, and so vaginal tumours are likely to represent metastasis from another site. Although breast cancer is a common malignancy, it rarely gives rise to vaginal metastases. In this study, we report a case of vaginal cancer diagnosed in a 65-year-old woman. Clinical examination showed the presence of a breast tumour, and ductal breast carcinoma was diagnosed by biopsy. Analysis of the vaginal tumour suggested that it was a metastasis. It was through the detection of the secondary tumour, complete gynaecologic examination, and complementary examinations that the primary site was correctly identified.

Keywords: Vaginal cancer, breast cancer, vaginal metastasis.

INTRODUCTION

Breast cancer is the most common neoplasm in women and a significant cause of death.[1] Approximately 3.5–10% of patients with newly diagnosed breast cancer present with concurrent metastatic disease.[2] This cancer often progresses because of distant metastases such as those in the bone, lung, pleura, brain, and liver. However, breast cancer metastasis to the vagina is rare.[1]

Secondary tumours of the vagina are more common than primary ones. The most common cause of metastatic disease is direct local invasion from the female urogenital tract.[3] A search of MEDLINE using search terms 'vaginal metastasis* AND breast cancer' yielded three cases reported in the literature. In two of these cases, lobular breast carcinoma was the primary disease, and in one case, ductal carcinoma was the primary disease. We report a case of vaginal metastasis from an invasive ductal breast carcinoma. At the time of diagnosis, bone involvement was also noted.

CASE

A 65-year-old African-American woman was admitted to our hospital because of pelvic and lower back pain and vaginal bleeding. Gynaecological examination revealed a 3 cm ulcerated tumour in the lower third of the anterior vaginal wall with a vesicovaginal fistula and a 2 cm painful, palpable inguinal lymph node. The uterine cervix and vulva were normal. On examination of the right breast, a hard 8 cm tumour was detected but axillary lymph nodes were not palpable.

The vaginal tumour was completely removed revealing a poorly differentiated ulcerated vaginal carcinoma (Figure 1). Immunohistochemical study showed that the tumour cells stained positive for cytokeratin (CK7), vimentin, and pan-cytokeratin (AE1/AE3), and negative for cytokeratin 20 (CK20), CEA, p63, CK5/6, and S100. However, the primary origin of the tumour could not be determined immunohistochemically.

Mammography showed the presence of a mass, 8 cm in maximum diameter, at the upper quadrant junction of the right breast (Figure 2). Biopsy indicated the presence of invasive ductal carcinoma (Figure 3). Immunohistochemical studies showed negative staining for the oestrogen receptor and positive staining for both the progesterone receptor (weak) and c-erbB2. Bone metastases

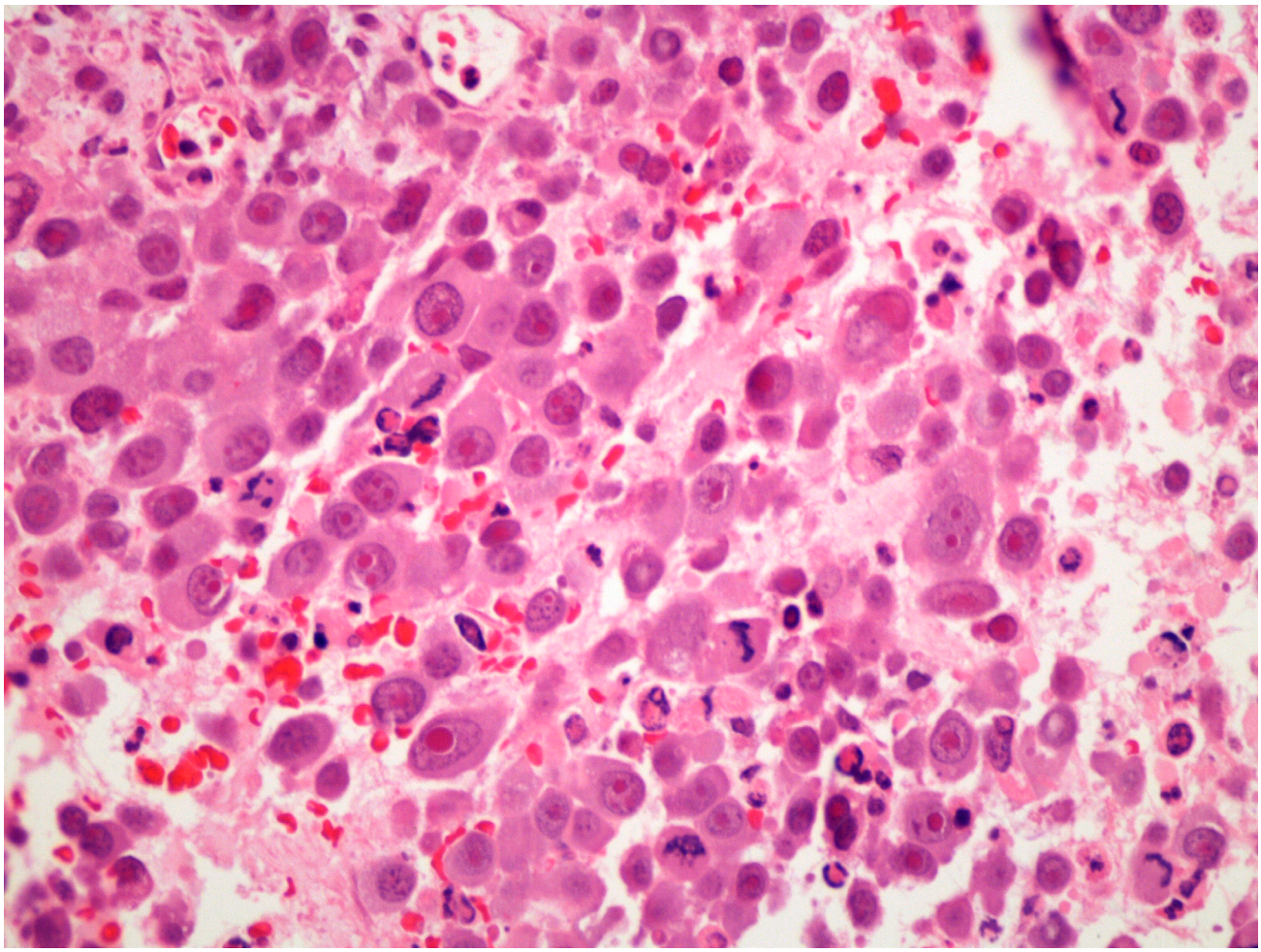

Figure 1. Histological examination of the vagina revealing poorly differentiated ulcerated carcinoma (staining haematoxylin and eosin; magnification 40×).

were detected on the right side of the frontal bone, shoulder joint, right scapula, third and fourth rib bones, ischium, hip joint, ankle joint, and transtrochanteric junction on bone scintigraphy. Abdominal ultrasonography did not indicate visceral metastases.

In this patient, breast cancer was classified as stage IV. The vaginal tumour was considered to be a metastasis from breast cancer, and it was suggested as the treatment with radiotherapy for vaginal and bone metastasis. As the vaginal tumour was completely removed and the patient achieved pain relief with medication (morphine), radiotherapy was not performed.

DISCUSSION

Primary cancers of the vagina are rare, predominantly affecting postmenopausal women and representing approximately 1–2% of all gynaecological cancers.[4] Histologically, two main types are defined: squamous cell carcinoma and adenocarcinoma. In most cases, squamous cell carcinoma is the histological type, and in these cases, vaginal intraepithelial neoplasia often precedes vaginal cancer.[4,5] Because of its rarity, the aetiological factors and prognosis of vaginal squamous cell carcinoma are not well known.[4] More than 80% of vaginal malignancies are metastatic cancers, and their detection may precede the diagnosis of the primary cancer.[3]

Our patient had a vaginal lesion in the lower anterior wall, with a vesicovaginal fistula and a painful palpable right inguinal lymph node. The location of the tumour determines the areas of lymphatic spread. The upper two-thirds of the vagina drain into the pelvic nodes of the obturator and internal and external iliac chains, and the lower third drains into the inguinal and femoral nodes.[6]

Although the diagnosis of this breast tumour was ductal carcinoma, lobular carcinoma seems to metastasise to the genital tract more frequently, probably due to haematogenous spread.[1]

Sometimes, discrimination between primary vaginal cancer and metastatic lesions is difficult.[3] An accurate diagnosis is important for appropriate therapy, prognosis, and follow-up. These cancers often occur as a metastasis from cervical cancer.[4] Vaginal cancer should initially be investigated as metastasis and should be considered as a primary tumour only after this investigation is complete.[3] In this case, diagnosis was based only on the absence of inferior vulvar abnormalities and superior cervical involvement and preceded the diagnosis of breast cancer.

Remote vaginal metastases may occur via lymphatic or haematogenous spread. There are isolated reports of metastases from extra-genital cancers, from colon, breast, pancreas, and small bowel cancers.[3]

Patients with advanced vaginal carcinoma should be treated with irradiation and concurrent cisplatin-based chemotherapy. This treatment option is chosen to avoid exenterative surgery, to preserve anatomy, and to treat lymph node metastasis.[7]

According to the existing treatment guidelines for metastatic breast cancer, removal of the primary tumour may be a therapeutic strategy in a distinctive subset of patients. These are represented by oligometastatic disease, characterised by solitary or few metastatic lesions, and usually in a single organ.[8]

Although many patients survive for several years after the diagnosis of distant metastases, curative treatment was not possible in this case; hence, the intent of the treatment was palliative. The optimal management of stage IV breast cancer is unclear. Although there is some evidence that surgery may be associated with improved overall survival, some authors believe that removal of the primary tumour could promote cell proliferation via suppression of cell-mediated immunity. Thus, there is no consensus about the value of surgery.[2]

Data on the treatment of vaginal metastases are limited, but most cases are treated with radiotherapy.[1] In this case, vaginal metastasectomy had limited prognostic relevance but helped to reduce bleeding. Metastasectomy in breast cancer is appropriate for patients in whom metastatic disease is limited to a solitary lesion or to multiple lesions at a single organ site. [9]

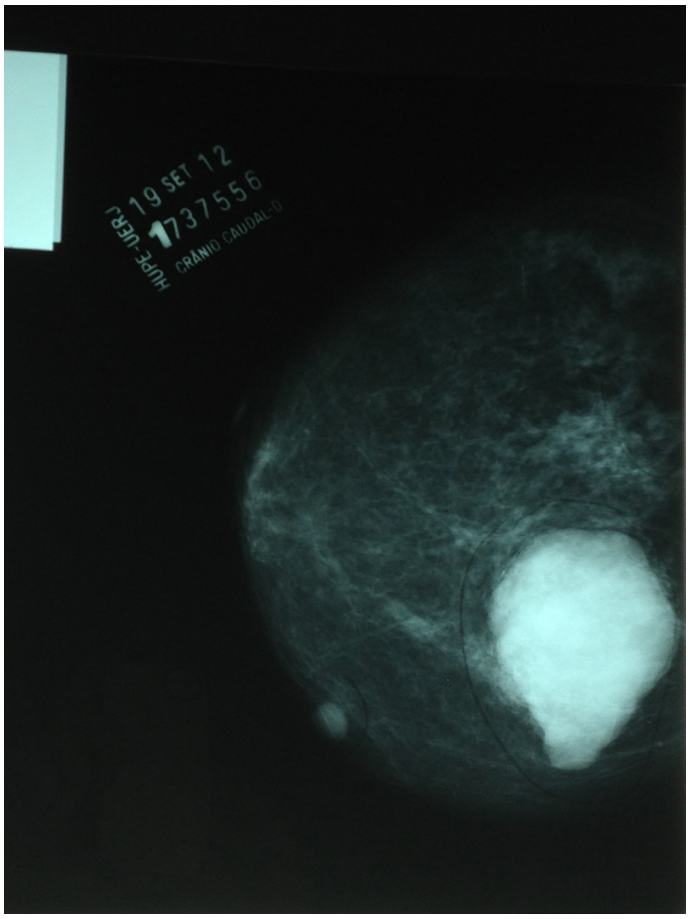

Figure 2. Mammography of right breast revealing an 8 cm mass.

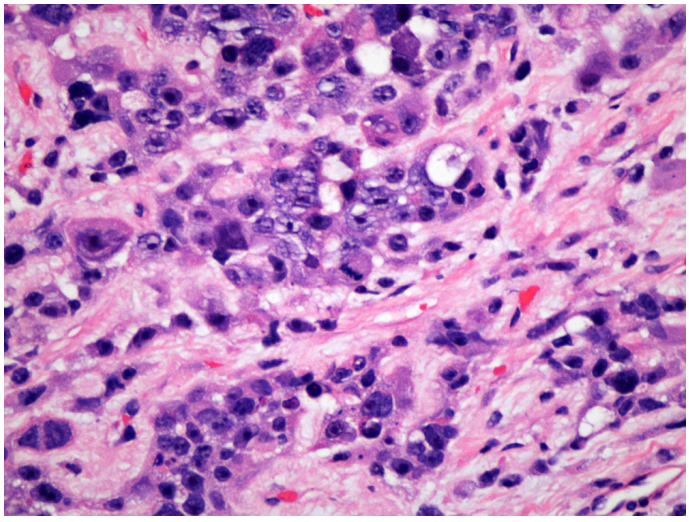

Figure 3. Histological examination of the breast revealing invasive ductal carcinoma (staining haematoxylin and eosin; magnification 40×).

Involvement of the bone generally suggests a better prognosis than involvement of visceral sites and does not affect the survival of patients. Good local control can be achieved with radiotherapy.[10]

Vaginal cancer should initially be considered as a secondary tumour until a complete investigation has been carried out, especially in cases, such as the one reported here, with an unusual histological type.

CONCLUSION

Breast cancer is very common, but association with vaginal metastases is rare. Although vaginal cancer is associated with lobular carcinoma more often, it must be considered as a possibility even when ductal carcinoma is present. This case study emphasises the importance of a complete examination in order to avoid the misdiagnosis of vaginal cancer, and to aid follow-up of patients with breast cancer.

REFERENCES

1. Bellati F et al. First case of isolated vaginal metastasis from breast cancer treated by surgery. BMC Cancer. 2012;12:479.

2. Samiee S et al. Excision of the primary tumour in patients with metastatic breast cancer: a clinical dilemma. Curr Oncol. 2012;19(4):e270–9.

3. Parikh JH et al. MR imaging features of vaginal malignancies. Radiographics 2008;28(1):49–63.

4. Hellman K et al. Protein expression patterns in primary carcinoma of the vagina. Br J Cancer. 2004;91(2):319–26.

5. Weiderpass E, Labreche F. Malignant tumors of the female reproductive system. Saf Health Work. 2012;3(3):166–80.

6. McMahon CJ et al. Lymphatic metastases from pelvic tumors: anatomic classification, characterization, and staging. Radiology. 2010;254(1):31–46.

7. Grigsby PW. Vaginal cancer. Curr Treat Options Oncol. 2002;3(2):125–30.

8. Pagani O et al. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst. 2010;102(7):456-63.

9. Singletary SE et al. A role for curative surgery in the treatment of selected patients with metastatic breast cancer. Oncologist. 2003;8(3):241-51.

10. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243s–9s.

NEW CERVICAL CANCER SCREENING GUIDELINES ON BOTH SIDES OF THE ATLANTIC

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ABSTRACT

Large population-based trials showed that the human papillomavirus (HPV) DNA test can be even more effective than Pap tests in preventing cervical cancer. Nevertheless, there are still many questions on how to implement HPV testing in screening, and particularly how to manage its lower specificity. In this paper, we compare the recommendations concerning the cervical cancer screening tools proposed by the most influential agencies and scientific societies in the last 3 years. We included six documents that evaluated the use of HPV DNA tests and formulated recommendations: the U.S. Preventive Services Task Force (USPSTF) systematic review and recommendations, the multi-societal USA, Canadian Task Force on Preventive Health Care (CTFPHC), the Dutch Health Council recommendations, and the Italian Health Technology Assessment report. The USPSTF review and the Canadian document concluded that there is no sufficient evidence to recommend HPV as a primary screening test, while the others conclude that HPV tests can be used as the primary screening test in patients starting from 30 years of age. The interval after a negative HPV test is 5 years for all the documents except the Dutch (5-10 year interval). The only relevant difference between recommendations is the role of cytology: co-testing in the USA, triage in Europe. The new European and USA guidelines on cervical cancer screening represent a further step towards protocol harmonisation, even if there are still some differences. This harmonisation was achieved through an evidence-based approach to the introduction of HPV as a primary test and through a general reduction of the intensity of screening protocols.

Keywords: Cervical cancer, HPV test, mass screening, guidelines.

INTRODUCTION

Cervical cancer is still a major cause of death among women around the world.[1] The burden of disease is concentrated in low and medium-income countries.[2] In most of the industrialised countries, incidence and mortality have decreased dramatically over the last few decades thanks to the diffusion of Pap test and screening programmes.[1,3,4] In fact, Pap tests make it possible to identify cellular abnormalities that are the expression of precancerous lesions. The treatment of precancerous lesions (high-grade cervical intraepithelial neoplasia, CIN2+) through non-invasive surgery is very effective in preventing cancer.[1]

The identification of persistent infection with oncogenic types of HPV as the necessary, but not sufficient, cause of cervical cancer[5] has led to the creation of two new tools for cancer prevention: a HPV test for screening, and a HPV vaccine to prevent infection.[6]

Since the first studies on HPV DNA test accuracy were conducted, it has been clear that the new test is more sensitive but less specific than the Pap test in identifying CIN2+.[7] Recently, several large population-based trials[8-12] showed that the HPV DNA test can be more effective than the Pap test in preventing cervical cancer. Nevertheless, there are still many questions on how to implement

the HPV test in screening, and particularly how to manage its lower specificity.[7,13]

In 2011-13, several new guidelines and recommendations on cervical cancer screening were published, all posing one of the main questions: whether the HPV DNA test should be recommended as primary screening test or not.[14-19] In this paper, we compare the recommendations concerning the cervical cancer screening tools proposed by the most influential agencies and scientific societies in the last 3 years.

METHODS

Sources of Information and Guidelines Selection

Although this is not a systematic review, in order to identify the most recent guidelines (since 2011) on population screening for cervical cancer, a literature search of the major databases was carried out. Specifically, we searched PubMed and general websites on healthcare and some specific sites for guidelines, and we studied the websites of several scientific societies of interest.

The aim was to identify all documents sufficiently updated and assess if they take into consideration the new main results of the European HPV test trials,[8-11] i.e. after 31st December 2010. Only documents with national or international relevance were included.

We included all the documents producing recommendations on screening in the general female population that included the HPV DNA test as primary screening test in their scope. Included documents are systematic reviews producing recommendations, guidelines, and HTA reports. This review is an update and a subset of a larger one that collected guidelines and recommendations for the cervical screening programme. Complete methods of the previous review are described on the 'Osservatorio Nazionale Screening' website (www.osservatorionazionalescreening.it). The search was updated on 31st July 2013.

Data Extraction

Two independent reviewers extracted the main conclusions and recommendations from the selected documents: target age, interval recommended, first level test, management of individuals according to first level test results, and assessment procedures (Table 1). The extraction forms were defined by a working group and then submitted to external advisors for review and piloting on two sample documents. The working group, the methods, and the list of external advisors are published online at www.osservatorionazonalescreening.it. Furthermore, specifically regarding whether or not to recommend the HPV as the primary screening test, the reviewers extracted the following items: main conclusions, studies included in the efficacy analysis, summary of the evidence and its level, summary of the recommendation and its strength. The extraction tables were then merged in a consensus process by the two reviewers.

RESULTS

We found eight documents that evaluated the use of the HPV DNA test and formulated recommendations, two of which were excluded due to their regional or local relevance.[20,21] Three documents were from the USA: one systematic review commissioned by the USPSTF,[18] a document reporting the USPSTF recommendations,[17] and the multi-societal recommendations by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology Screening Guidelines.[16] Two other documents were from Europe: the Dutch Health Council recommendations,[14] i.e. a proposal formulated by the council to the Government, and the Italian health technology assessment (HTA) report,[19] which includes in its second chapter a draft of the unpublished European Guidelines. The sixth document reports the recommendations of the Canadian Task Force on Preventive Health Care.[15]

All the documents considered studies on accuracy, in particular one previous systematic review[7] and one large randomised trial,[22] but the use of this information in the production of the recommendations was not uniform. Regarding efficacy data, the trials available are the same for all the reviews: five European trials (NTCC,[11,23] POBASCAM,[8,24] ARTISTIC,[9,25] SWEDESCREEN,[10] Finland[26,27]) and one trial from rural India.[12] All the reviews considered the study by R. Sankaranarayanan et al.[12] separately because the intervention and the comparator were 'once-in-a-lifetime' screenings, and the results

cannot be used to estimate the effect in industrialised countries.

Some important observational studies were also considered by some reviews, in particular the pooled analysis of European cohort studies,[28] used by all of the documents to establish the best screening interval, and the study by Katki et al.,[29] as confirmation of the effectiveness in real practice (considered only by USPSTF recommendations and multi-societal guidelines).

Another difference among the reviews regarding the available data was the follow-up data on invasive cancer in the POBASCAM trial,[24] which have been included in all of the reviews except the first USPSTF, because it was not published when the authors closed the literature search.

The analyses concentrated on two main points: 1) is the HPV test more sensitive than the Pap test for CIN3+ at baseline screening? 2) If so, is there a decrease in the CIN3+ detection at following rounds in women who underwent HPV screening compared to those screened with the Pap test at baseline, i.e. were the excess lesions found with HPV at baseline persistent? These two points take into account efficacy and safety at the same time, i.e. the sum of the CIN2+ detected at first and subsequent rounds directly measure the relative overdiagnosis[30] and the reduction of CIN3, and in particular, cancers at subsequent rounds measure the efficacy. The two points are clearly treated as distinct from each other in the two European documents and in the multi-societal document, while the USPSTF and the Canadian documents do not clearly separate the two points.

The separate analysis of baseline data (providing information on sensitivity), and subsequent rounds (testing the efficacy in reducing incidence), led the European and the multi-societal documents not to consider the Finnish trial in the efficacy analysis, since the second round data have never been published. The USPSTF systematic review and the Canadian document, instead, considered the Finnish trial even for the efficacy endpoint. Given the absence of second round results, the Finnish trial is the only European trial that did not register a reduction in the incidence of CIN3 and cancer during follow-up.

Table 2 reports the general conclusions, evidence syntheses, and recommendations of the six documents on the use of the HPV DNA test as primary screening. Two documents[15,18] conclude that there is no convincing evidence for the use of HPV, while the others conclude that HPV can be recommended: the Italian, the Dutch, and the multi-societal documents state that HPV is preferable to or more effective than Pap tests, while the USPSTF recommendations consider the two equivalent.

Table 1 summarises the main recommendations given by the six documents on screening. The starting age varies from 21 (USA) to 30 (NL), while the stopping age is 65 for all except for the Netherlands, where it is 60. All the documents recommend shifting the primary screening test from Pap tests to HPV at the age of 30. The interval to be deemed HPV negative is 5 years for the USA and Italy, while for the Netherlands it is 5 years until age 40, then 10 years. Co-testing is recommended in the 2012 USA guidelines, and triage is recommended in Italy and the NL.

Women with cytology and HPV testing positive are referred to colposcopy in all four documents (Figure 1). Furthermore, in the USA documents, there is also the option to type the HPV and to refer the women who are infected by HPV16/18 to colposcopy. For women testing positive with HPV and negative for cytology, the recommendations differ slightly:

- In the USA, women are referred to 1-year for a HPV test and cytology; women testing either HPV positive or cytology positive are referred to colposcopy.[31]

- In Italy, women are referred to 1-year for HPV only. If the test is still positive, women are referred to colposcopy; if negative, to 5-year screening.

- In the Netherlands, women are referred to 6-month cytology control; if cytology is positive, they are referred to colposcopy; if cytology is negative, they are referred to 5-year HPV tests.

Finally, all the documents state that the recommendations should be updated in the short-term because new evidence will be produced by trials on stand-alone HPV tests[16,18] and on triage biomarkers.[14,16,19] In addition, updates will eventually take into

account the impact of vaccinated cohorts on screening performance.[19]

DISCUSSION

Despite the fact that the six documents are based on almost the same body of evidence, four documents[14,16,17,19] recommend the use of HPV as primary screening and two do not.[15,18] The level of evidence and the grade of recommendations are essentially the same for the four documents recommending the use of HPV test: the highest level of evidence and the strongest grade of recommendation. The only difference is the comparison with Pap test screening: equivalence for the USPSTF document (a Pap test every 3 years is equal to HPV every 5 years) and superior for the other documents.

To better understand why the conclusion of the first USPSTF document was not to recommend HPV, while the second reached the opposite conclusion, it is worth analysing in detail the process that led to the recommendations. The recommendations are essentially identical to the multi-societal ones, but are clearly in contrast with the conclusions of the systematic review, commissioned by the USPSTF itself, published just 4 months earlier. In the final paragraph of the recommendations, it is explained that the debate[32] started after the publication of the systematic review and the publication of new evidence. In particular, the update of POBASCAM follow-up[24] and the observational data of the Kaiser Permanente[29] led to a different interpretation of the whole evidence body and consequently to different recommendations. Obviously, the synchronicity with the multi-societal work resulted in a larger scientific consensus on the final conclusions.

When analysing the interpretation of the available evidence provided by the two documents not recommending the HPV in detail, two main justifications for their conclusion emerge. Firstly, as the trials adopted different protocols, the authors decided not to pool the results. Thus, there is no statistical power on the reduction of cancer incidence. Secondly, as most of the trials adopted a co-testing strategy, the strongest evidence is for this strategy. However, it produces an enormous increase in unnecessary work-up, adding harm due to HPV false positives to that of the Pap test false positives. The conclusions in the USPSTF systematic review are also supported by considerations on the scarce applicability of 5-year intervals in the setting of opportunistic screening in the USA.

The interpretation of the evidence by the USA documents recommending HPV differs as: 1) the overall evidence that HPV can further reduce cancer incidence is strong; 2) the strongest evidence is for co-testing, and; 3) the unnecessary work up for false positive can be controlled with longer intervals and the final balance of benefit and harm is in favour of HPV.

The interpretation given by the two European documents is different still as: 1) the CIN3 and cancer reduction in HPV arms versus Pap test arms is consistent in all the studies, and does not depend on the protocol adopted (co-testing or HPV stand-alone or HPV followed by triage); 2) as the most efficient strategy is HPV followed by triage, this the recommended strategy. It must be noted that all the trials used in the systematic reviews to estimate HPV efficacy were conducted in Europe,[8,11,26] where the co-testing strategy has never been considered a plausible option for a priori cost-effectiveness considerations (it is clearly inefficient). Thus, the trials adopted a co-testing strategy[8-11,33] only as a precautionary principle or to allow the comparison of multiple strategies. However, once confirmed that the number of lesions found and treated at baseline in HPV negative women was negligible, all the data analyses focused on measuring the effectiveness of a triage strategy or a stand-alone strategy.[25,34,35]

The interpretation given by the European documents allows a more complete use of the evidence, but also requires more assumptions concerning the natural history of the disease. The validity of the assumptions and the appropriateness of the ancillary evidence use are crucial. In this case, the assumption that main differences in cancer incidence between the two arms were due to the adoption of HPV and not to other characteristics of the protocol adopted was strongly supported by the natural history of the disease,[1,5] and was consistent with the results of the trials themselves.

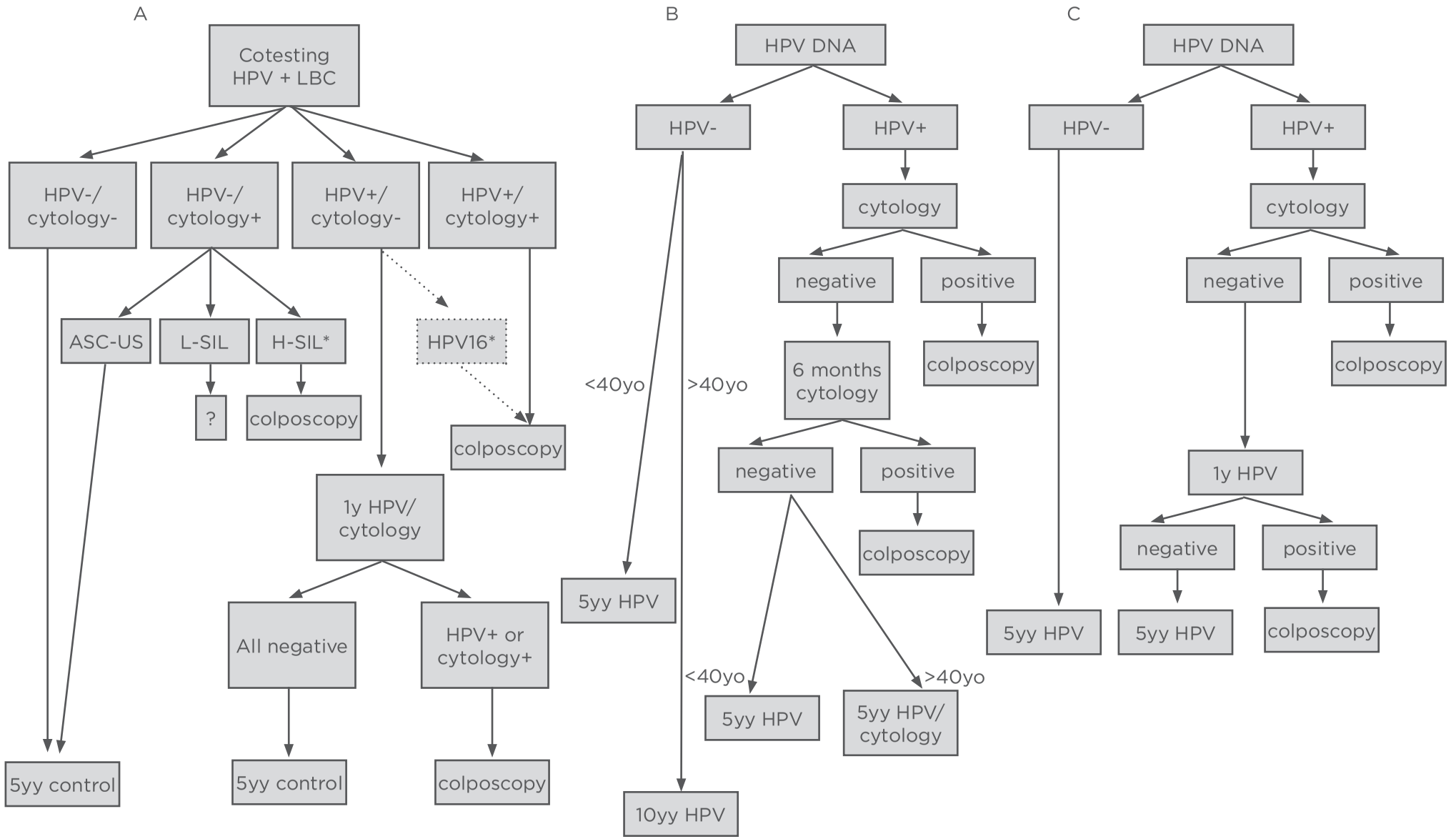

Figure 1. Simplified flowcharts of the HPV screening-based algorithms in the four documents recommending the HPV DNA test as a primary screening test.

A. USPSTF recommendations and multi-societal USA Guidelines[16,17,29]

B. Recommendations of the Dutch Health Council[14]

C. Italian HTA report[19]

			Screening target population			Target age for HPV primary test				Management of abnormal results			
Country	Year	Agency	Start	Stop	HPV for primary screening recommended	Start	Stop	Screening interval for HPV negative	Cytology and HPV combination strategy	HPV+ cyto+	HPV+ cyto-	HPV- cyto+	HPV typing recommended
USA	2011	USPSTF[18]	21	65	no			-	-	-	-	-	-
USA	2012	USPSTF[17]	21	65	yes	30	65	5yy	Cotesting (a)	Colposcopy	1 year HPV + cytology	?	-
USA	2012	ACS AS-CCP ASCP[16]	21	65	yes	30	65	5yy	Cotesting (a)	Colposcopy	1 year HPV + cytology	ASC-US -> 5yy; L-SIL -> ?;(c) H-SIL -> colpo	HPV 16 and/ or 18 may be referred to colposcopy even if cyto -
Canada	2013	Canadian Task Force[15]			no			-	-	-	-	-	-
Italy	2012	Ministry of Health[19]	25	64	yes	30-35	64	5yy	Triage (b)	Colposcopy	1 year HPV	-	Only in research
Netherlands	2011	Health Council[14]	30	60	yes	30	60	30-40 - >5yy >40 - >10yy	Triage (b)	Colposcopy	1 year HPV + cytology	-	-

(a) Both cytology and HPV performed simultaneously as primary screening test.
(b) Cytology preformed sequentially only in case of HPV positive results.
(c) Non-management for HPV negative L-SIL was reported in the multi-societal guidelines in 2012, according to the recommendations by the American Society for Colposcopy and Cervical Pathology (ASCCP) published in 2013, these women would be referred to 1-year control with HPV and cytology.

Table 1. Synthesis of the recommendations of the six documents about cervical cancer screening.

Table 2. Document conclusions, evidence statements with related level of evidence, and recommendations with related grade about HPV-DNA as primary screening test for cervical cancer reported in the six documents.

Document	Conclusion	Included studies for efficacy analysis	Evidence	HPV recommendation
USPTF Moyer (2012)[17]		NTCC[11,23] ARTISTIC[9,25] POBASCAM (only preliminary data)[8] SWEDESCREEN[10] Finnish[4]	30-65 years: The benefits of screening with co-testing (cytology/HPV testing) every 5 years outweigh the harms. **Evidence level: high**	Screen with cytology every 3 years or co-testing (cytology/human papillomavirus testing [HPV]) every 5 years. **Grade of recommendation: A** (Offer or provide this service)
			<30 years: The potential harms of screening with HPV testing (alone or with cytology) outweigh the potential benefits. **Evidence level: adequate**	USPTF recommend do not screen with HPV test. **Grade of recommendation: D** (Discourage the use of this service)
USPTF Withlock (2011)[18]	'...more complete evidence is needed before HPV-enhanced primary screening is widely adopted for women aged 30 years or older.'	NTCC[11,23] ARTISTIC[9,25] POBASCAM (including follow up)[24] SWEDESCREEN[10] Finnish[4] Kaiser Permanente[29]		
HTA Italian Ronco (2012)[19]	'There is clear scientific evidence that a screening based on validated tests for the DNA of oncogenic HPV as primary test and applying an appropriate protocol is more effective than screening based on cytology in preventing invasive cancers of the uterine cervix. In addition, it entails a limited - if any - increase of the undesired effects...'	NTCC[11,23] ARTISTIC[9,25] POBASCAM (including follow up)[24] SWEDESCREEN[10]		"... the crucial requirement to introduce HPV-based screening programmes is the capacity to guarantee the application of appropriate screening protocols."

Netherlands Health Council recommendations (2011)[14]	The Committee concludes that there is clear evidence that hrHPV screening is more effective than cytology as a primary screening method. As hrHPV screening detects high-grade CIN and cervical cancer earlier, the present frequency of screening can be reduced.	NTCC[11,23] ARTISTIC[9] POBASCAM (including follow up)[24] SWEDESCREEN[10]		The Committee recommends a switch to hrHPV screening. The continued use of cytology as a primary screening test, alongside hrHPV testing, is not efficient.
ACS-ASCCP-ASCP (2012)[16]		NTCC[11,23] ARTISTIC[9,25] POBASCAM (including follow up)[24] SWEDESCREEN[10] Finnish[4] Kaiser Permanente[29]	30-65 years: absolute increase in CIN3+ detection in first round (ranging from 17% to 31%). Absolute decrease in cancer detected at second round (ranging from 0.03% to 0.05%). **Evidence level: high**	30-65 years: should be screened with cytology and HPV testing ('cotesting') every 5 years (preferred) or cytology alone every 3 years (acceptable). **Grade of recommendation: cotesting preferred**
			<30 years: Because of the high prevalence of HPV in women aged younger than 30 years, HPV testing should not be used to screen women in this age group due to the potential harms **Evidence level: insufficient**	<30 years: HPV testing should not be used to screen women in this age group **Grade of recommendation: PAP test acceptable**
Canadian TFPHC (2013)[15]	'These updated recommendations do not address screening with tests for human papillomavirus virus, because there is not yet sufficient data on its effect on mortality and incidence of invasive carcinoma.' 'However, we will revisit this issue as new data become available.'	NTCC[11,23] ARTISTIC[9,25] POBASCAM (including follow up)[24] SWEDESCREEN[10] Finnish[4] Kaiser Permanente[29]	**Evidence level: ?**	No use of HPV as primary screening test. More research is needed on the effectiveness and optimal use of HPV screening in decreasing the incidence of and mortality due to cervical cancer. **Grade of recommendation: ?**

Looking at the last 20 years of cervical cancer screening on both sides of the Atlantic, we can see a progressive alignment towards less intensive protocols in order to reduce overdiagnosis and undesired effects,[36] and to increase efficiency. Before 2010, the starting age in the USA was 18,[37] there was no stopping age, and the interval was 1 year. In the same period, the starting age in Europe was 22-30,[38] the stopping age 60-65, and the interval was 3-5 years. In 2010, the USA introduced a stopping age, increased starting age to 21, and increased the interval to 2-3 years.[39] In 2012 in the USA and Europe, with the introduction of HPV testing, the starting age was identical (at least for HPV, i.e. 30), as were the interval and the stopping age.[16,17] The only difference was the role of cytology: co-testing in the USA, triage in Europe.

Public health interventions such as screening programmes involve the whole health system. Recommendations on mass screening, therefore, cannot be based only on the efficacy of the intervention, but must also take into account its acceptability by health operators and population, its feasibility, and whether it is affordable. Organisational and cost barriers are explicitly mentioned by some of the documents[14,19] even if in some cases they are not clearly distinguished from the efficacy evaluation.[18,32] Thus, all of the conclusions drafted by the guidelines must be considered valid within their context (with the exception of the USPSTF systematic review,[18] which was superseded by the recommendations in 2012[17]) and applied judiciously.

For those countries with a national health system, such as many European countries, the question is not what guidelines are the best, but which guidelines are in place in that specific country, which programme will be implemented by the health system, and what the role of each health professional is in this programme.

CONCLUSION

The new European and U.S. guidelines on cervical cancer screening represent a further step towards protocol harmonisation, even if there are still some differences. This harmonisation was achieved through an evidence-based approach to the introduction of HPV as a primary test and through a general reduction of the intensity of screening protocols.

REFERENCES

1. WHO, International agency for research on cancer. IARC handbooks of cancer prevention. Cervix Cancer Screening. Vol 10 (2005). Lyon: IARC Press.

2. IARC. Globocan 2008. Cancer fact sheet: Cervical Cancer Incidenceand Mortality Worldwide in 2008. http://globocan.iarc.fr/factsheets/cancers/cervix.asp (accessed6/4/2012).

3. Quinn M et al. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinelycollected statistics. BMJ. 1999;318(7188):904-8.

4. Anttila A. Cervical cancer screening is effective - the Finnish experience. Entre Nous. WHO Regional Office, Copenhagen. 2007;64:26-8.

5. Walboomers JM et al. Human papillomavirusis a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9.

6. zurHausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002;2(5):342-50.

7. Cuzick J et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine. 2008;26(Suppl10):K29-41.

8. Bulkmans NW et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet. 2007;370(9601):1764-72.

9. Kitchener HC et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol. 2009;10(7):672-82.

10. Naucler P et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. 2007;357(16):1589-97.

11. Ronco G et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010;11(3):249-57.

12. Sankaranarayanan R et al. HPV screening for cervical cancerin rural India. N Engl J Med. 2009;360(14):1385-94.

13. Cuzick J et al. New technologies and procedures for cervical cancer screening. Vaccine. 2012;30(Suppl 5):F107-16.

14. Health Council of the Netherlands. Population screening for cervical cancer. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/07E.

15. Canadian Task Force on Preventive Health Care, Pollock S et al. Recommendations on screening for cervical cancer. CMAJ. 2013;185(1):35-45.

16. Saslow D et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol. 2012;137(4):516-42.

17. Moyer VA et al. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;156(12):880-91.

18. Whitlock EP et al. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med.

2011;155(10):687-97.

19. Ronco G et al. Health technology assessment report. Use of liquid-based cytology for cervical cancer precursors screening. Epidemiol Prev. 2012;36(5Suppl2):e1-33.

20. Schwaiger C et al. Current guidelines for cervical cancer screening. J Am Acad Nurse Pract. 2012;24(7):417-24.

21. Murphy J et al. Cervical screening: a guideline for clinical practice in Ontario. J Obstet Gynaecol Can. 2012;34(5):453-8.

22. Mayrand MH et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med. 2007;357(16):1579-88.

23. Ronco G et al. Results at recruitment from a randomised controlled trial comparing human papillomavirus testing alone with conventional cytology as a primary cervical cancer screening test. J Natl Cancer Inst. 2008;100:492-501.

24. Rijkaart DC et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol. 2012;13(1):78-88.

25. Kitchener HC et al. ARTISTIC: a randomised trial of human papillomavirus

(HPV) testing in primary cervical screening. Health Technol Assess.

2009;13(51):1-150.

26. Leinonen M et al. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. J Natl Cancer Inst. 2009;101:1612-23.

27. Anttila A et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. BMJ. 2010;340:c1804.

28. Dillner J et al. Long-term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ. 2008;337:a1754.

29. Katki HA et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011;12(7):663-72.

30. Ronco G et al. HPV testing for primary cervical cancer screening. Lancet. 2007;370(9601):1740-2.

31. Massad LS et al. updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol. 2013;121(4):829-46.

32. Ronco G et al. Screening for cervical cancer. Ann Intern Med. 2012;156(8):604-5.

33. Ronco G et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst. 2006;98(11):765-74.

34. Ronco G et al. Efficacy of HPV-based Screening for Preventing Invasive Cervical Cancer: follow-up of European randomised controlled trials. Lancet. In-press.

35. Rijkaart DC et al. Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. Int J Cancer. 2012;130(3):602-10.

36. Sawaya GF. Rightsizing cervical cancer screening: comment on "Cervical cancer screening with both human papillomavirus and Papanicolaou testing vs Papanicolaou testing alone". Arch Intern Med. 2010;170(11):985-6.

37. U.S. Preventive Services Task Force, Screening for cervical cancer. January2003. http://www.ahrq.gov/clinic/uspstf/uspscerv.htm. (accessed 20/3/2010).

38. European Commission, Arbyn M et al. (eds.), in European Guidelines for Quality Assurance in Cervical Cancer Screening 2nd edition. (2008), Luxembourg:Office for Official Publications of the European Communities, pp. 1-291.

39. (ACOG) Committee on Practice Bulletins – Gynecology. ACOG practice bulletin no. 109: cervical cytology screening. Obstet Gynecol. 2009;114:1409–20.

INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF PANCREATIC ADENOCARCINOMA: A REVIEW

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ABSTRACT

Pancreatic cancer remains one of the leading causes of cancer deaths. Despite improvements in imaging, surgical techniques, chemotherapy agents, and radiation techniques, the prognosis for patients with pancreatic adenocarcinoma remains poor. Traditionally, radiotherapy (RT) has been utilised as neoadjuvant, adjuvant, or definitive treatment, and represents an important therapeutic option in pancreatic adenocarcinoma. Intensity-modulated radiation therapy (IMRT), a more recent RT technique, has the potential to deliver an adequate dose to the tumour volume with a minimal dose to the surrounding critical structures such as duodenum, small intestine, liver, kidneys, and spinal cord. This article provides a review about the role of IMRT in the treatment of pancreatic cancer, concerning clinical outcomes such as toxicity, local control, and overall survival.

Keywords: Pancreatic cancer, intensity-modulated radiotherapy, toxicity, outcome.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer deaths in Europe. In addition, a recent cancer mortality prediction for the year 2013 confirmed that pancreatic cancer is the only cancer which has not had an improvement in European mortality.[1]

Radiation therapy (RT) associated with chemotherapy and surgery has been shown to be an important treatment modality for patients with pancreatic cancer in both adjuvant and neoadjuvant settings.[2-3] However, one of the main limitations of RT is the high radiosensitivity of the surrounding organs at risk, such as duodenal mucosa, small intestine, liver, kidneys, and spinal cord. Because of this, RT is often markedly associated with an increase of severe toxicity especially when a dose escalation to the tumour volume is prescribed.

Intensity-modulated radiation therapy (IMRT) is a recent technique in the delivery of RT. The use

of IMRT is increasingly aimed at generating a more conformal coverage to the tumour volume compared to standard techniques, while maximising the sparing of normal and surrounding critical tissues.

In an aim to investigate the current clinical role of IMRT in the treatment of pancreatic carcinoma, a review of recently published literature was performed.

RESULTS

Clinical trials between 2001 and 2013 have been selected, analysed, and reported (Table 1, 2, and 3). Only studies investigating clinical outcomes by the use of IMRT for adjuvant and/or locally advanced pancreatic cancer treatment have been included. Studies evaluating only dosimetric parameters have been excluded.

Conventional Fractionated Radiotherapy

The clinical advantage of conventional fractionated IMRT was shown in some retrospective analysis (Table 1). Compared with conformal RT, IMRT was able to reduce the mean dose to the liver, kidneys, stomach, and small bowel, in 25 patients.[4] 80% of patients experienced Grade ≤2 acute upper gastrointestinal (GI) toxicity. At a median follow-up of 10.2 months, no local failure was noted compared with resected patients. The median survival and distant metastasis-free survival of the 24 patients with adenocarcinoma was 13.4 and 7.3 months respectively. Late liver Grade 4 toxicity occurred in 1/14 patients with a follow-up over 6 months.

Yovino S et al.[5] revised data from 46 patients with pancreatic/ampullary cancer treated with concurrent 5-fluorouracil (FU) and IMRT. Rates of acute GI toxicity for this series of patients were compared with those from RTOG 97-04,[6] treated with three-dimensional conformal techniques. Patients receiving IMRT showed a significant reduction in the incidence of Grade 3-4 nausea and vomiting (0% versus 11%, p=0.024) and diarrhoea (3% versus 18%, p=0.017).

Patterns of first failure were analysed by the same authors in the following study of 71 patients treated with adjuvant IMRT and concurrent chemotherapy.[7] At median follow-up of 24 months, the local failure rate was 69%. Distant metastases, predominantly in the liver, were the most frequent failure pattern (49%). 14 patients (19%) developed locoregional failure. Median overall survival (OS) was 25 months.

Abelson JA et al.[8] reviewed data of 47 patients (29=resected; 18=unresectable) treated by IMRT plus concurrent 5-FU. Four patients (9%) developed Grade ≥3 acute toxicity, and four (9%) developed Grade 3 late toxicity. For adjuvant patients (median survival=1.7 years), the 1 and 2-year OS rate was 79% and 40%, respectively. The 1 and 2-year recurrence-free survival (RFS) rates were 58% and 17%; local-regional control (LRC) rates were 92% and 80%, respectively. For unresectable patients, the 1-year OS, RFS, and LRC rates were 24%, 16%, and 64%, respectively, with a median OS of 7.7 months.

Image-guided radiotherapy (IGRT) offers the possibility of safe margin reduction to generate the planning target volume (PTV) given the reduced interfraction movement through daily imaging. The combination of daily imaging to the steep dose gradient of IMRT may potentially further improve the toxicity of abdominal irradiation. The use of IG-IMRT was investigated in a retrospective analysis of 41 patients, conducted to evaluate the feasibility of ultrasound-based IG-IMRT.[9] Upper GI toxicity Grade ≤2 occurred in 38 patients (92.7%) and lower GI toxicity Grade ≤2 in 39 patients (95.1%). Upper GI Grade 3 toxicity was reported in three patients (7.3%) whereas Grade 4 lower GI toxicity in two patients (4.9%). Mean daily image-guidance corrective shifts were less than 10 mm in all directions, supporting the conclusion that a safety margin reduction and a moderate dose escalation should be afforded by implementation of IG-IMRT.

Trials investigating the role of IMRT with conventional fractionation and concurrent molecular targeted therapy were also conducted (Table 1). In a prospective dose de-escalation trial, patients with resected pancreatic adenocarcinoma received erlotinib and capecitabine concurrently with IMRT.[10] 13 patients were enrolled in two dose levels: erlotinib 150 mg and capecitabine 1600 mg/m^2 without interruption (DL 1) and erlotinib 100 mg and capecitabine 1600 mg/m^2, Monday to Friday (DL-1). Six of the seven evaluable patients at DL-1 required treatment interruption or dose reduction and four completed planned treatment.

Table 1. Intensity-Modulated Radiotherapy with conventional fractionation in the treatment of pancreatic carcinoma.

	Study design	Pts (n)	Dose RT (Gy)	Dose/ fraction (Gy)	ConcCT	ENI	Acute Toxicities ≥3 (%)	Clinical response (%)	Local Control (%)	Median OS (m)	OS (%)	Late Toxicities ≥3 (%)
Milano MT, (2004)[4]	Retrospective analysis	25 R:8; LA :17	R: 45-50.4 LA: 50.4-59.4	1.8	5FU	Yes	Leukopenia 16 Anaemia 4 GI 20	*PR: 50 CR: 10 SD: 30	LF: 4 (LA)	Overall: 13.4 R: 14.3 LA: 9.3	Overall: 1y: 55 2y: 22 R, 1y: 83 2y: 50 LA, 1y: 40 2y: 8	Liver 4
Yovino S, (2011)[5]	Retrospective analysis	46 R :31; LA:15	R: 45 LA: 50.4-59.4	1.8	5FU or Cap	Yes	GI 4	NS	NS	R: 24.8 LA: 9.7	NS	GI 4
Yovino S, (2012)[7]	Retrospective analysis	71 R	54 -64.8,	1.8	Cap or Gem	Yes	GI 8	NE	LF: 19	25	NS	GI 7
Abelson JA, (2012)[8]	Retrospective analysis	47 R :29; LA :18	R: 44-55.8 LA: 39.6-59.4	1.8 1.8-2	Cap or 5FU	Yes	GI 9	NS	LF: 21 (R)	R: 20.4 LA: 7.7	R, 1y: 79 2y: 40 LA, 1y: 24	GI 9
Fuss M, (2007)[9]	Retrospective analysis	41 R :17; LA :24	45-64	1.8-2	Cap or Gem	Yes	GI 12	NS	NS	10.3 R: 10.8 LA: 10.0	38	NS
Ma WW, (2010)[10]	Dose de-escalation trial	13 R	50.4	1.8	Erlotinib + Cap	Yes	Neutropenia 8 GI 38	NE	NS	NS	NS	GI 8
Pipas JM, (2012)[12]	Phase II	37 (33 evaluable) R:4; BR: 23; LA: 6	45- 54	1.8	Cetuximab + Gem	Yes	Neutropenia 68 Thrombocytopenia 32 Anaemia 3 GI 59	PR: 30 SD: 61	LF: 12 (R)	17.3 R: 24.3	NS	NS

Pts: patients; concCT: concomitant chemotherapy; ENI: elective nodal irradiation; R: Resected/resectable; LA: Locally advanced/unresectable; Gem: gemcitabine; 5FU: 5-fluorouracil; Cap: Capecitabine; GI: gastrointestinal; NS: not stated; NE: Not evaluable; PR: partial response; CR: Complete response; SD: stable disease; LP: local progression; LF: local failure; m: months; y: year(s).

Note: GI toxicity includes anorexia, nausea, vomiting, dehydration, diarrhoea, bleeding, small bowel obstruction. *10 LA patients with survival >3 months.

	Study design	Pts (n)	Dose RT (Gy)	Dose/ fraction (Gy)	ConcCT	ENI	Acute Toxicities≥3 (%)	Clinical response (%)	Local Control (%)	Median OS (m)	OS (%)	Late Toxicities ≥3 (%)
Ben-Josef E, 2012 [13]	Phase I-II	50 LA	50- 60	2- 2.4	Gem	No	Neutropenia 56 Thrombocytopenia 13 Anaemia 11 GI 22	PR: 33 SD: 67	LP: 17	14.8	2ys: 30	NS
Vainshtein JM, 2012 [14]	Phase I-II	38 LA	50- 60	2- 2.4	Gem	No	NS	NS	LP: 29	15.2	2ys: 26.6	NS

Pts: patients; concCT: concomitant chemotherapy; ENI: elective nodal irradiation; LA: Locally advanced/unresectable; Gem: Gemcitabine; GI: Gastrointestinal; NS: Not stated; Partial response: PR; Stable disease: SD; LP: Local progression; m: months; y: year(s).
Note: GI toxicity includes anorexia, nausea, vomiting, dehydration, diarrhoea, bleeding, small bowel obstruction.

Table 2. Dose-esclation Intensity-Modulated Radiotherapy in the treatment of pancreatic carcinoma.

Table 3. Intensity-Modulated Radiotherapy with altered fractionation in the treatment of pancreatic carcinoma.

	Clinical trials	Pts (n)	Dose RT (Gy)	Dose/ fraction (Gy)	ConcCT	ENI	Acute Toxicities≥3 (%)	Clinical response (%)	Local Control (%)	Median OS (m)	1 y OS %	Late Toxicities ≥3 (%)
Crane CH, 2001[15]	Phase I	5 LA	33	3.3	Gem	Yes	Leukopenia 100 Trombocytopenia 20 Anaemia 20 GI 60	PR: 20	LP: 67	NS	NS	NS
Bai YR, 2003[16]	Phase I	21 LA (16 evaluable)	3D-CRT: 30+ IMRT: 21-30	2 3	Gem\or 5FU	Yes	Neutropenia 10 Trombocytopenia 5 Anaemia 5	PR: 31	NS	NS	35	NS
Koong AC, 2005[17]	Phase II	19 LA	IMRT: 45+ SRS: 25	1.8	5FU or Cap	Yes	GI 11	SD: 100	LP: 6	7.7	15	11
Ben-Josef E, 2004[18]	Retrospective analysis	15 R: 7; LA: 8	R: 45-54 LA: 54	25 1.8-2.16 2.16	Cap or Celecoxib	Yes	GI 7	NS	LF: 14 (R)	NS	LA: 69	NS
Ji JS, 2010[19]	Retrospective analysis	19 LA	50.4-55	1.8-2.2	Cap	Yes	0	PR: 53 SD: 47	LP: 0	6.5	36.8	NS
Chang JS, 2012[20]	Retrospective analysis	39 LA	45-60	1.8-2.2	Gem or Cisplatin+ Gem or S1	No	Leukopenia 29 Trombocytopenia 16 Anaemia 10 GI 5	PR: 53 SD: 39	LR: 25	21.2	61.5	GI 26
Son SH, 2012[21]	Retrospective analysis	12 LA	45 or 50	3 or 2.5	5FU	No	Neutropenia 17 Trombocytopenia 8	PR: 58 SD: 42	LF: 8	12.1	NS	NS

Pts: patients; concCT: concomitant chemotherapy; ENI: elective nodal irradiation; R: Resected/resectable; LA: Locally advanced/unresectable; Cap: Capecitabine; Gem: Gemcitabine; 5FU: 5-Fluorouracil; GI: Gastrointestinal; NS: Not stated; Partial response: PR; Stable disease: SD; LP: Local progression; LF: Local failure; m: months; y: year(s).

Note: GI toxicity includes anorexia, nausea, vomiting, dehydration, diarrhoea, bleeding, small bowel obstruction.

The dose-limiting toxicities were neutropaenia, diarrhoea, and rash. Six patients enrolled in DL-1 completed the planned treatment. Only minor toxicities such as fatigue, elevated liver enzymes, and anorexia were shown with less GI toxicity if compared to conformal RT.[11]

Finally, the efficacy of combination cetuximab plus gemcitabine with IMRT, as neoadjuvant treatment in patients with LAPC, was investigated in a Phase II trial.[12] 37 patients were enrolled, and 33 were assessable for response. 25 patients (76%) underwent resection and 23 (92%) had negative surgical margins. Grade 3 (<10% viable tumour cells) or IV (no viable tumour cells) tumour kill, including two (8%) pathological complete responses (pCR), were found in 24% of resected tumours. Overall, median survival was 17.3 months, compared to 24.3 for resected patients.

Dose-Escalation Trials

Furthermore, to confirm that dose escalation intensification by IMRT could improve local control and survival, two Phase I/II studies were conducted (Table 2).[13-14] Dose levels were escalated to 60 Gy. In the first study, 50 patients with unresectable pancreatic cancer were accrued.[13] Grade 3-4 GI acute toxicities were observed in 11 patients (22%) and the recommended dose was 55 Gy. Median and 2-year OS were 14.8 months and 30%, respectively. 12 patients (24%) underwent resection (10 R0, 2 R1) with a median survival of 32 months.

38 patients were subsequently analysed by the same authors[14] showing a median survival of 15.2 months and 2-year OS was 26.6% Median progression-free survival (PFS) was 8.6 months. Local and distant progression occurred in 11 patients (29.0%) and 25 patients (65.8%), respectively. The ability of CA19-9 to act as a disease-monitoring biomarker was also demonstrated.

Altered Fractionated Radiotherapy

The tolerability of IMRT with altered fractionations was also evaluated (Table 3). In one dose escalation trial,[15] hypofractionated (33 Gy/11 fractions) IMRT was delivered in combination with gemcitabine. Five patients were enrolled and treated in two dose levels. All three patients in the first cohort (gemcitabine at 350 mg/m^2) suffered from myelosuppression and upper GI toxicity. Therefore, a lower gemcitabine dose (250 mg/m^2) was later administered. The acute toxicity profile was confirmed and further investigations were expected.

21 patients with locally advanced pancreatic cancer (LAPC) were enrolled in the following Phase I trial.[16] Patients received doses between 21 Gy to 30 Gy in 7-10 fractions by IMRT following 2 weeks after a conventional RT of 30 Gy/15 fractions. The total escalation tumour dose was 51, 54, 57, 60 Gy, respectively. 16 patients who had completed the RT treatment plan were evaluated. No patient suffered more than Grade 3 acute toxicities.

The efficacy of IMRT in patients with LAPC was confirmed in a Phase II study.[17] 19 patients were enrolled to receive IMRT (45 Gy, 1.8 Gy/day) and concurrent 5-FU followed by a boost with stereotactic radiosurgery (SRS, 25 Gy, single fraction). 16 patients completed the planned therapy. Although Grade 3 toxicity was observed in 2 patients, 15 patients were free from local progression until death with a median OS of 33 weeks.

A low toxicity profile of IMRT was also confirmed in a retrospective analysis of 15 patients.[18] A total dose of 45 or 54 Gy, 1.8 or 2.16 Gy/fraction was delivered in adjuvant or neoadjuvant setting, respectively. Concurrent capecitabine and celecoxib were given to seven patients (73%). Grade 1/2 nausea or vomiting developed in eight patients (53%) and Grade 1/2 haematologic toxicity in nine patients (60%). Only one patient had a gastric ulceration that responded to medical management (Grade 3 GI toxicity). With a median follow-up of 8.5 months, no deaths but one local relapse (14%) were reported in resectable patients. The 1-year survival rate of uresectable patients was 69%.

19 patients with LAPC were enrolled in a study where capecitabine was concurrently administrated with Helical Tomotherapy (HT), an advanced IMRT with integrated CT imaging[19] (total dose=50-55 Gy, 1.8-2.2 Gy/fraction). Overall, in-field response rate was 42.3%. Partial responses were achieved in 53.3% of the pancreatic masses and 25% of regional lymph nodes. With a median follow-up of 6.5 months, no lesion showed in-field progression. Only Grade 1 toxicities were developed.

Data of 39 patients with LAPC treated with RT using high-dose HT (median dose =58.4 Gy) and concomitant chemotherapy were retrospectively reviewed.[20] 29 patients (74%) received gemcitabine during HT. Acute toxicities were acceptable with no GI toxicity higher than Grade 3. Late GI toxicity ≥Grade 3 occurred in 10 patients (26%). The median follow-up was 15.5 months for the entire cohort, and 22.5 months for the surviving patients. Eight patients (21%) were converted to resectable status and a pCR was found in one patient. The 1 and 2-year local PFS rates were 82.1% and 77.3% respectively. The median OS and PFS were 21.2 and 14.0 months, respectively.

Finally, Son et al.[21] evaluated the technical feasibility of hypofractionated HT with concurrent and sequential chemotherapy in 12 patients with LAPC. The total dose delivered was 45 Gy/15 fractions or 50 Gy/20 fractions. Grade 2 acute toxicity was developed in seven patients (58%). No patient showed Grade 3 or worse toxicity. Clinical partial response was reported in 58% of patients and 42% had stable disease. One patient (8%) experienced local progression and 9 patients (75%) experienced distant progression (median follow-up=31.1 months). No patient had regional failure. PFS and OS were 7.6 and 12.1 months, respectively.

DISCUSSION AND CONCLUSIONS

Pancreatic adenocarcinoma was wrongly considered in the past as a radioresistant tumour. On the contrary, although more data are needed before firm conclusions can be drawn, this tumour can be locally controlled by RT with a total dose of 45-50 Gy as documented by the ability to achieve a complete pathological response rate up to 20%.[18,20,22] Unfortunately, a safe administration of this dose is not easy due to the presence of several radiosensitive surrounding organs; kidneys, liver, small intestine, stomach, duodenum, and spinal cord. Thus, RT for pancreatic cancer currently represents a technological challenge.

In this analysis, we evaluated toxicity and clinical outcomes obtained by the use of IMRT in the last 10 years. As reported, IMRT was able to reduce the irradiation of normal tissue with acceptable grade of acute and late GI toxicity. Unfortunately, most data comes from retrospective analysis or preliminary Phase I or II trials. The only study that compared the toxicity among patients undergoing three dimensional-RT and patients undergoing IMRT, actually compared two different patient populations, one from a randomised and the other from a cohort study.[5] For these reasons the results of this comparison cannot be considered totally credible and generalisable. Moreover, a great heterogeneity regarding recruitment criteria (periampullary, biliary duct and/or pancreatic carcinoma; resectable and/or LAPC), treatment target volumes (elective nodal irradiation or not, different margins for CTV and PTV) and response and toxicity evaluation criteria, was observed.

Based on these considerations, new prospective studies with quality protocols for outcomes evaluation, more standardised contouring guidelines,[23-24] and cost-effective evaluation[25] are needed to better define any clinical benefit of IMRT and to resolve some emerging controversy in healthcare economy related to the technology innovations in radiation oncology and clinical outcomes.

REFERENCES

1. Malvezzi M et al. European cancer mortality predictions for the year 2013. Ann Oncol. 2013;24(3):792-800.

2. Goodman KA, Hajj C. Role of radiation therapy in the management of pancreatic cancer. J Surg Oncol. 2013;107(1):86-96.

3. Morganti AG et al. A systematic review of resectability and survival after concurrent chemoradiation in primarily unresectable pancreatic cancer. Ann Surg Oncol. 2010;17(1):194-205.

4. Milano MT et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys. 2004;59(2):445-53.

5. Yovino S et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. Int J Radiat Oncol Biol Phys. 2011;79(1):158-62.

6. Regine WF et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. JAMA. 2008;299(9):1019-26.

7. Yovino S et al. Analysis of local control in patients receiving IMRT for resected pancreatic cancers. Int J Radiat Oncol Biol Phys. 2012;83(3):916-20.

8. Abelson JA et al. Intensity-modulated radiotherapy for pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2012;82(4):e595-601.

9. Fuss M et al. Image-guided intensity-modulated radiotherapy for pancreatic carcinoma. Gastrointest Cancer Res. 2007;1(1):2-11.

10. Ma WW et al. A tolerability and pharmacokinetic study of adjuvant erlotinib and capecitabine with concurrent radiation in resected pancreatic cancer. Transl Oncol. 2010;3(6):373-9.

11. Czito BG et al. Increased toxicity with gefitinib, capecitabine, and radiation therapy in pancreatic and rectal cancer: phase I trial results. J Clin Oncol. 2006;24(4):656-62.

12. Pipas JM et al. Neoadjuvant cetuximab, twice-weekly gemcitabine, and intensity-modulated radiotherapy (IMRT) in patients with pancreatic adenocarcinoma. Ann Oncol. 2012;23(11):2820-7.

13. Ben-Josef E et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2012;84(5):1166-71.

14. Vainshtein JM et al. Prognostic significance of carbohydrate antigen 19-9 in unresectable locally advanced pancreatic cancer treated with dose-escalated intensity modulated radiation therapy and concurrent full-dose gemcitabine: analysis of a prospective phase 1/2 dose escalation study. Int J Radiat Oncol Biol Phys. 2013;86(1):96-101.

15. Crane CH et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. Int J Gastrointest Cancer. 2001;30(3):123-32.

16. Bai YR et al. Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: results of feasibility study. World J Gastroenterol. 2003;9(11):2561-4.

17. Koong AC et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2005;63(2):320-3.

18. Ben-Josef E et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;59(2):454-9.

19. Ji JS et al. Helical tomotherapy with concurrent capecitabine for the treatment of inoperable pancreatic cancer. Radiat Oncol. 2010;5:60.

20. Chang JS et al. High-dose helical tomotherapy with concurrent full-dose chemotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2012;83(5):1448-54.

21. Son SH et al. The technical feasibility of an image-guided intensity-modulated radiotherapy (IG-IMRT) to perform a hypofractionated schedule in terms of toxicity and local control for patients with locally advanced or recurrent pancreatic cancer. Radiat Oncol. 2012;7:203.

22. Patel M et al. Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer. J Surg Oncol. 2011;104(2):155-61.

23. Caravatta L et al. Clinical target volume delineation including elective nodal irradiation in preoperative and definitive radiotherapy of pancreatic cancer. Radiat Oncol. 2012;7:86.

24. Goodman KA et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. Int J Radiat Oncol Biol Phys. 2012;83(3):901-8.

25. Murphy JD et al. Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer. Cancer. 2012;118(4):1119-29.

KEY ADVANCES IN THE SYSTEMIC THERAPY FOR SOFT TISSUE SARCOMAS: CURRENT STATUS AND FUTURE DIRECTIONS

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ABSTRACT

Soft tissue sarcomas (STS) represent a heterogeneous group of diverse neoplasms of mesenchymal origin. Once relapsed from standard therapy, STS patients have limited treatment options especially those that present with advanced or metastatic disease. In this review article, we highlight recent clinical data that led to the US Food and Drug Administration (FDA) approval of pazopanib (Votrient®) for STS and regorafenib (Stivarga®, BAY 73-4506) in gastrointestinal stromal tumours. We also review ongoing safety/efficacy data for trabectedin (Yondelis®, ET-743), and data from clinical studies of ridaforolimus (AP23573; MK-8669) and palifosfamide (ZIO-201). We provide a list of some promising ongoing trials in soft tissue sarcomas including first line studies of TH-302 and trabectedin. Finally, our article delves into recent advances in our understanding of the molecular pathogenesis of STS and novel therapies that might be explored as treatment options for specific STS histologies.

Keywords: Sarcoma, soft tissue sarcoma, gemcitabine, pazopanib, regorafenib.

INTRODUCTION

Soft tissue sarcomas (STS) represent a heterogenous group of diverse neoplasms of mesenchymal origin. According to recent Surveillance, Epidemiology, and End Results (SEER) database, approximately 11,000 men and women will be diagnosed with STS in 2013 accounting for <1% of all newly diagnosed cancers. Many patients with these tumours have distant metastases at presentation. It is estimated that around 4,000 patients with STS will die in 2013.[1] The major histologic subtypes include leiomyosarcoma (LMS), liposarcoma (LPS), synovial sarcomas, undifferentiated pleomorphic sarcomas, and malignant nerve sheath tumours. Historically, LMS, synovial, and undifferentiated pleomorphic sarcomas are considered chemosensitive, while the others are chemoresistant. Traditional cytotoxic drugs adriamycin (Rubex®) and ifosfamide (Mitoxana®) have been the mainstays of treatment in certain STS patients with advanced disease. The National Comprehensive Cancer Network (NCCN) Guidelines recommend anthracycline monotherapy, or combination with ifosfamide as the first line treatment for most histologic subtypes (category 2A and 2B evidence).[2] There has been a dearth of well-designed randomised trials in the area of metastatic STS, mostly due to the heterogeneity of the group and a lack of identification of specific dominant druggable molecular targets. Locally advanced and metastatic STS thus remain an area of significant unmet medical need. Results of recently published clinical studies in advanced or metastatic STS are described in the following sections.

Gemcitabine (Gemzar®) and Docetaxel (Taxotere®)

The gemcitabine and docetaxel combination is often used as a second line therapy in STS. This

combination is more active in uterine LMS and undifferentiated high-grade pleomorphic sarcoma than other subtypes. The possible synergistic effect of gemcitabine, a DNA synthesis inhibitor and docetaxel, a tubulin stabiliser that induces apoptosis, was explored in a Phase II trial of LMS patients in 2002. Out of 34 patients enrolled, complete response (CR) was observed in 3 patients, and partial response (PR) was observed in 15 patients for an overall response rate (ORR) of 53%.[3] A randomised Phase II study in 2007 showed an improvement in median progression-free survival (PFS) for the combination treatment (6 months) versus gemcitabine therapy alone (3 months). The objective response rate of 16% versus 8% and the median overall survival (OS) of 18 months versus 12 months in favour of the combination arm was demonstrated in a population that included several subtypes, but was especially pronounced in uterine LMS.[4] In this study, a fixed infusion rate of gemcitabine was used based on prior reports of a favourable pharmacokinetic profile and efficacy in STS.[5]

In a study of LMS patients, the French TAXOGEM study found no differences in treatment with single agent gemcitabine or the combination of gemcitabine and docetaxel. The objective response rates were 19% in the gemcitabine group, 24% in the gemcitabine plus docetaxel group for uterine LMS, and 14% and 5% for non-uterine LMS. The median progression-free survival times were not significantly different for either group: 5.5 months and 4.7 months for uterine LMS, and 6.3 months versus 3.8 months in non-uterine LMS.[6] Although the SARC and TAXOGEM studies differed in study design, patient selection, and slightly different dose intensities, and schedules of fixed dose gemcitabine, it is unclear whether any of these factors could explain the differences in outcome. Despite these differences, gemcitabine with or without docetaxel are preferred agents in first or second line treatment of a wide variety of STS subtypes, especially LMS.

Pazopanib (Votrient®)

Agents against the vascular endothelial growth factor (VEGF) axis have been well-studied in STS. Sorafenib (Nexavar®), a tyrosine kinase inhibitor of platelet-derived growth factor receptors (PDGFR), VEGFR-1, VEGFR-2, and VEGFR3, was shown to be minimally active in high-grade STS patients who had 0-1 prior therapies. Response rates of less than 5% were noted, but PFS at 3 months and 6 months were 53% and 22%, respectively. 61% of patients required dose reductions due mostly to dermatologic toxicities.[7] The highest response rates in this study were in angiosarcoma patients (14% PR). Sunitinib (Sutent®), another multi-targeted TKI was tested in STS patients who had received 0 to 3 prior therapies. There was one response in 48 patients and the 4-month progression-free survival was 22%. This study included patients with rare sarcomas such as giant cell tumours, alveolar soft part sarcoma, chordoma, and desmoplastic small round blue cell tumours.[8] Thus, other than angiosarcoma and other less common subtypes, VEGF-TKI's have not been shown to be highly active in patients with STS.

Pazopanib however, is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR-1, 2 and 3), platelet derived growth factor receptor (PDGFR-A and B), and v-kit Hardy Zuckerman 4 feline sarcoma viral oncogene homolog (c-kit) that demonstrated activity in Phase II studies in non-adipocytic sarcomas. It was initially US Food and Drug Administration (FDA)-approved for advanced renal cell carcinoma in 2009. Recently, pazopanib received approval by the FDA in patients with advanced soft tissue sarcoma (except adipocytic STS or gastro-intestinal stromal tumours) who have received prior chemotherapy. The approval was based on a randomised double blind placebo-controlled multicenter trial of patients with metastatic STS who had received an anthracycline containing regimen or were ineligible for it. Patients were randomised 2:1 to either pazopanib (800 mg PO QD) or placebo. The median overall survival was 12.6 months in the pazopanib arm and 10.7 months in the placebo arm (HR 0.87, 95% CI 0.67-1.12). Overall progression-free survival (PFS) in the intent to treat population was 4.6 months in the pazopanib group versus 1.6 months in the placebo group. The OS benefit correlates well with the PFS benefit of 3 months. Unfortunately, the trial was not powered to detect a statistically significant 3-month OS difference in the two arms. The OS data could also be confounded by the fact that patients received post-study therapy with trabectedin (25% versus 32%), gemcitabine (17% versus 23%) taxane (10% versus 18%) and ifosfamide (10% versus 17%). Nevertheless, the PFS benefit was seen across the pre-specified

subgroup analyses, and was independent of the number of prior chemotherapy agents and tumour bulk. The most common Grade 3/4 adverse events experienced by ≥5% of patients on pazopanib were fatigue, diarrhoea, hypertension, and decrease in appetite. The most common (≥20%) observed adverse events (all grades) were fatigue, diarrhoea, nausea, decreased appetite, vomiting, tumour pain, hair colour changes, musculoskeletal pain, headache, dysgeusia, dyspnoea, and skin hypopigmentation.[9] The demonstration that the VEGF pathway could be exploited for therapeutic benefit in the majority of STS has opened the future for combined treatments with targeted and non-targeted agents.

Regorafenib (Stivarga®, BAY 73-4506)

As opposed to the recent approval of anti-VEGF agents in non-GIST STS, gastrointestinal stromal tumours (GISTs) are especially responsive to the VEGF-TKI, Sunitinib (Sutent®). The activity of sunitinib as second line therapy in GIST is well-established. The use of sequential anti-VEGF strategies has been effective in improving progression-free survival in renal cell carcinoma, and this approach is now promising in treating unresectable advanced or metastatic GIST. Regorafenib is an oral multi-tyrosine kinase inhibitor of VEGFRs 2 and 3, and RET, Kit, PDGFR and Raf kinases. In 2013, the FDA expanded the use of regorafenib to treat patients with advanced inoperable GIST unresponsive to imatinib (Gleevec®) or sunitinib. The approval was based on an international randomised double blind, placebo controlled trial of 199 patients with histologically confirmed metastatic or unresectable GIST who experienced disease progression while on sunitinib. The primary endpoint of median PFS was significantly better for the regorafenib group at 4.8 months compared to 0.9 months for patients receiving placebo (HR 0.27, 95% CI 0.19-0.39, p<0.0001). The most common drug-related adverse events (Grade 3 or higher) were hypertension, hand-foot skin reaction, and diarrhoea. Serious adverse events (SAEs) occurred infrequently (<1%) and included liver damage, severe bleeding, blistering and peeling of the skin, very high blood pressure, heart attack, and perforations in the intestine.[10]

Gemcitabine Plus Dacarbazine (DTIC)

A Phase II study of dacarbazine (DTIC) with or without gemcitabine in soft tissue sarcomas showed a PFS of 4.2 months in the gemcitabine plus DTIC arm (n=57) compared to 2 months in the DTIC alone (n=52) arm (HR 0.58, 95% CI 0.39-0.86, p=0.005). Median overall survival was 16.8 months in the gemcitabine plus DTIC arm versus 8.2 months in the DTIC arm (HR 0.56, 95% CI 0.36 to 0.90, p=0.014). Overall response rate was 12 months in the combination arm versus 4% for the DTIC arm (p=0.16). A Cox regression analysis of prognostic factors for survival in the study population identified histology (LMS versus others) as significant prognostic factor for PFS and OS. Median PFS and OS were 4.9 and 18.3 months respectively for the LMS subtype in the gemcitabine and DTIC group versus 2.1 months and 7.8 months for those with non-leiomyosarcomatous subtypes. The combination of DTIC and gemcitabine was generally well-tolerated. Granulocytopenia was the most common Grade 3/4 haematologic toxicity. Febrile neutropenia was observed in 9% patients in the combination arm versus 6% in the DTIC arm.[11]

Trabectedin (ET-743, Yondelis®)

Trabectedin is a novel marine antineoplastic alkaloid with a unique mechanism of action. It binds to the DNA minor groove and interferes with transcription-coupled nucleotide excision repair thereby inducing lethal DNA strand breaks, a mechanism that lends itself to increased activity in translocation-related sarcomas including myxoid LPS.[12,13]

It was approved in the European Union as an orphan drug for the treatment of advanced soft tissue sarcoma in patients who have failed therapy with anthracycline and ifosfamide. The approval was based on a Phase II study in LMS and LPS patients who had failed anthracycline plus ifosfamide therapy and multiple other supporting studies.[14] The primary endpoint, time to progression (TTP) was 2.3 months in the qwk 3-hour group (N=134) versus 3.7 months in the q3wk 24-hour group (N=132). This compared well with the 3.4 month TTP in the initial 24-hour group (from 3 other Phase II studies). The PFS was 2.1 (95% CI 1.9-3.4) months in the qwk 3-hour group versus 3.5 (95% CI 2.0-4.5) months in the q3wk 24-hour group and 2.7 (95% CI 1.7 – 3.7) months in the Initial 24-hour group. The most common grade 3-4 adverse events (AEs) in the q3wk 24-hour group were increased alanine aminotransferase, (ALT) (12%), neutropenia (12%), increased aspartate aminotransferase (AST)

(8%), and dyspnoea, fatigue, nausea, and vomiting (7% each). In addition, rhabdomyolysis leading to death was seen in five patients (0.5%) in the integrated safety database.[8] The recent data from the expanded access program of trabectedin in patients with incurable soft tissue sarcoma demonstrated longer overall survival in patients with LPS (median of 16.2 months, 95% CI 14.1 – 19.5) versus other histologies (median 8.4 months, 95% CI 7.1-10.7) for the 903 patients evaluable for OS. More importantly, out of 1,895 total patients enrolled, grade 3 or 4 AEs exhibited by ≥5% of patients included nausea, increased ALT, neutropenia, anaemia, thrombocytopenia, and fatigue. These were consistent with previous studies.[15] The results of first line trabectedin versus doxorubicin-based treatment in translocation-related sarcomas are expected soon. In addition, a large multi-institutional international Phase III study comparing trabectedin versus dacarbazine has recently reached its accrual goals for LPS that have failed two prior therapies (NCT01343277).

Ridaforolimus (AP23573; MK-8669)

The dysregulation of mammalian target of rapamycin (mTOR) pathway has been observed in many tumour types.[16] Ridaforolimus, a mTOR inhibitor, was found to show activity in advanced sarcomas in a Phase II study of 193 patients with 3% partial responses and 25% stable disease response.[17] Ridaforolimus was not approved by the FDA as maintenance therapy, in patients with either soft tissue or bone sarcomas who had achieved at least a stable disease (SD) with prior chemotherapy, primarily because a minimal 3 week difference in PFS and significant toxicity including pneumonitis. A pivotal trial comparing ridaforolimus or placebo maintenance for patients with soft tissue sarcoma or bone sarcomas who had achieved SD, partial response (PR) or complete remission (CR) with prior chemotherapy showed a median PFS of 17.7 weeks in the ridaforolimus arm versus 14.6 weeks in the placebo arm (HR 0.69, p<0.0001). The median OS in the ridaforolimus arm was 90.6 weeks versus 85.3 weeks in the placebo arm (HR 0.93, p=0.46). Significant adverse events including pneumonitis (10% versus 0.6%), renal failure (10% versus 1%) and hypersensitivity reaction (10% versus 2%) were reported more often in the ridaforolimus arm.[18]

Palifosfamide (ZIO-201)

The neurotoxicity and nephrotoxicity of ifosfamide are primarily thought to result from the toxic metabolites of ifosfamide, chloroacetaldehyde and acrolein. Palifosfamide is a tris formulation of the functional active metabolite of ifosfamide, isophosphoramide mustard.[19] The PICASSO-3 study investigating the combination of palifosfamide and doxorubicin versus doxorubicin alone in metastatic STS, was halted by the sponsor due to lack of PFS benefit. Median PFS was 5.98 months in the combination arm versus 5.23 months in the doxorubicin arm.[20] Even though the Data Monitoring Committee recommended following the patients for the secondary endpoint of assessing overall survival, the sponsor statement indicates otherwise.[21]

ONGOING STUDIES

Table 1 lists some important ongoing studies in soft tissue sarcoma. A Phase IIb/III study comparing the efficacy of trabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in patients with advanced or metastatic soft tissue sarcoma (EORTC, NCT01189253) is currently enrolling patients. A study investigating trabectedin or dacarbazine for patients with advanced LPS or LMS who have been previously treated with an anthracycline containing regimen is currently underway (NCT01343277). An expanded access program for non-L-type sarcomas is also open in the US (NCT00210665), which will allow evaluation of adverse events.

TH-302 is a pro-drug that is activated in the hypoxic tumour environment to its active form bromo-isophosphoramide mustard (Br-IPM), a potent DNA alkylating agent. The Phase III trial comparing the combination of TH-302 and doxorubicin versus doxorubicin alone (NCT01440088) was initiated based on favourable Phase II data showing a median PFS 6.7 (95% CI 6.2 to 8.1) months for the combination arm compared to median PFS of 21.5 (95% CI 16.0 to 27.6) months for the doxorubicin arm. Dose limiting toxicities were Grade 4 thrombocytopenia and Grade 3 infection with Grade 4 neutropenia.[22]

Based on the regorafenib data in GIST, a randomised, double-blind, placebo-controlled, Phase II study evaluating the efficacy and safety of regorafenib in patients with histologically

Table 1. Important ongoing clinical studies in soft tissue sarcoma.

Investigation	STS type	Primary End-point	Line of therapy	NCI clinicaltrials.gov #
TH-302 and doxorubicin versus doxorubicin	STS excluding GIST	OS	First	NCT01440088
Trabectedin versus doxorubicin	Chemosensitive STS subtypes	PFS	First	EORTC NCT01189253
Trabectedin versus dacarbazine	Liposarcoma and leiomyosarcoma	OS	Second	NCT01343277
Gemcitabine + Pazopanib versus Gemcitabine + docetaxel	STS excluding LPS, bone sarcoma and GIST	PFS	Second	NCT01593748
Cabazitaxel versus prolonged infusional ifosfamide	Dedifferentiated LPS	PFS	Second	EORTC NCT01913652
Regorafenib versus placebo	LPS, LMS, synovial sarcoma	PFS	Second	NCT01900743
Eribulin versus dacarbazine	LMS and adipocytic sarcoma	OS	Third	NCT01327885
Trabectedin (open access)	Non L-type STS	Adverse events	After standard therapy	NCT00210665

proven metastatic and/or unresectable soft tissue sarcoma (STS) after failure or intolerance to doxorubicin (or other anthracycline) is currently recruiting patients (NCT01900743).

Previous studies indicate that the incidence of somatic p53 gene mutation is low in most sarcomas (<20%).[23] Mouse double minute 2 homolog (MDM2) binds and inactivates p53 thereby promoting the ubiquitination and proteasomal degradation. The Phase II study evaluating the MDM2 inhibitor from Roche in soft tissue sarcomas (NCT01605526) was recently completed, with data from the study expected to be released in the near future. Another approach to inhibit the export of p53 and other tumour suppressor proteins could involve the use of nuclear export inhibitors. KPT330, an inhibitor of nuclear export is currently undergoing Phase I testing in soft tissue sarcomas (NCT01896505).

The FDA approval of sipuleucel-T (PROVENGE®) and CTLA-4 antibody ipilimumab (YERVOY™) for metastatic castration resistant prostate cancer and late-stage melanoma respectively has renewed interest in exploring immunomodulatory therapy for the treatment of STS. In addition, there has been a renaissance in the immunotherapy trials with programmed death 1 (PD-1) protein, a T cell co-inhibitory receptor, and one of its ligands, PD-L1 and the promising data in melanoma and non-small cell lung cancer.[24,25] Since the clinical trial of inhaled GM-CSF for osteosarcoma patients with recurrent lung metastasis showed no significant clinical benefit or even an immune response,[26] there are not many investigations of immunotherapies in STS. A current ongoing study from the University of Miami is investigating the use of adjuvant vaccination with autologous dendritic cells with our without gemcitabine (to inhibit myeloid derived suppressor cells) is currently recruiting patients (NCT01803152). In addition, a clinical trial using autologous, activated dendritic cells for intra-tumoural injection for all solid tumours has been initiated across multiples sites in the US that is open to STS patients as well (NCT01882946).

Mifamurtide (Mepact), also known as liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE), is an activator of macrophages and monocytes and has been approved for the treatment of osteosarcoma in Europe but not in the USA. The clinical trials in patients with osteosarcomaresulted in 8% and 13% improvement in 6 and 5-year overall survivals, when added to chemotherapy in non-metastatic and metastatic patients with osteosarcoma, respectively.[27]

Recent advances in the understanding of molecular pathways underlying the pathogenesis of soft tissue sarcomas have identified various genes that are overexpressed in different STS subtypes. These include MDM2 gene amplification in well-differentiated and de-differentiated LPS,[28] NAB2-STAT6 translocation in solitary fibrous tumour,[29] angiopoietin-TIE pathway in angiosarcoma,[30] BCL-2 overexpression in synovial sarcoma,[31] CDK-4 amplification in alveolar rhabdomyosarcoma,[32] ALK aberrations in rhabdomyosarcoma,[33] and lack of arginosuccinate synthase in various sarcomas.[34]

CONCLUSION

The tremendous advances in our understanding of tumour biology at the 'multi-omic' level that includes the genomic, proteomic, transcriptomic, and the post-transcriptomic levels has brought to forefront novel cellular pathways, aberrations and targets for therapeutic intervention across multiple adult tumour types. However, the wide-ranging diversity of STS subtypes, both from a histologic as well as a molecular perspective and the rarity has hindered our understanding of the disease and the ability to develop more effective therapies. Doxorubicin held the distinction of being the only FDA-approved drug in STS for over two decades. The approval of pazopanib is a significant incremental advance, and provides an important treatment option for patients who progress on doxorubicin (with or without ifosfamide). Soft tissue sarcomas still represent a significant unmet medical need. Ongoing clinical studies along with advances in immunotherapy and targeted therapies offer the potential for more effective treatment strategies in the future.

REFERENCES

1. Howlader N et al (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.

2. NCCN Clinical Practice Guidelines Sarcoma. (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) (accessed 9th September, 2013).

3. Hensley ML et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol. 2002;20(12):2824-31.

4. Maki RG et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol. 2007;25(19):2755-63.

5. Patel SR et al. Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. J Clin Oncol. 2001;19(15):3483-9.

6. Pautier P et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist. 2012;17(9):1213-20.

7. Maki RG et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009;27(19):3133-40.

8. George S et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. J Clin Oncol. 2009;27(19):3154-60.

9. van der Graaf WT et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-86.

10. George S et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. J Clin Oncol. 2012;30(19):2401-7.

11. García-Del-Muro X et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish group for research on sarcomas study. J Clin Oncol. 2011;29(18):2528-33.

12. D'Incalci M et al. Preclinical and clinical results with the natural marine product ET-743. Expert Opin Investig Drugs. 2003;12(11):1843-53.

13. Grosso F et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. Lancet Oncol. 2007;8(7):595-602.

14.http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000773/human_med_001165.jsp (EPAR - Yondelis) (accessed 9th September, 2013).

15. Samuels BL et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. Ann Oncol. 2013;24(6):1703-9.

16. Wan X et al. The biology behind mTOR inhibition in sarcoma. Oncologist. 2007;12(8):1007-18.

17. Chawla SP et al. Updated results of a phase II trial of AP23573, a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcoma. J Clin Oncol. 2006;24(suppl18):9505a.

18. Demetri GD et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol. 2013;31(19):2485-92.

19. Jones B et al. Anticancer activity of stabilized palifosfamide in vivo: schedule effects, oral bioavailability, and enhanced activity with docetaxel and doxorubicin. Anticancer Drugs. 2012;23(2):173-84.

20. Ryan CW et al. PICASSO 3: A phase 3 international randomized double-blind, placebo-controlled study of doxorubicin plus palifosfamide vs dox plus placebo for patients in first-line for metastatic soft tissue sarcoma. Abstract 3802, ESMO 2013.

21. http://ir.ziopharm.com/releasedetail.cfm?ReleaseID=750983, (accessed 9th September, 2013).

22. Ganjoo K et al. TH-302 maintenance following TH-302 plus doxorubicin induction: the results of a Phase 2 study of TH-302 in combination with doxorubicin in soft tissue sarcoma. CTOS. 2012.

23. Taubert H et al. Soft tissue sarcomas and p53 mutations. Mol Med. 1998;4(6):365-72.

24. Brahmer J et al. Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455-65.

25. Wolchok J et al. Nivolumab plus Ipilimumab in advanced melanoma. N Engl J Med. 2013;369:122-33.

26. Arndt CA et al. Inhaled granulocyte-macrophage colony stimulating factor for first pulmonary recurrence of osteosarcoma: effects on disease-free survival and immunomodulation. A report from the Children's Oncology Group. Clin Cancer Res. 2010;16(15):4024-30.

27. Anderson PM et al. Mifamurtide in osteosarcoma--a practical review. Drugs Today (Barc). 2010;46(5):327-37.

28. Dei Tos AP et al. Coordinated expression and amplification of the MDM2, CDK4, and HMGI-C genes in atypical lipomatous tumours. J Pathol. 2000;190:531–6.

29. Robinson DR et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet. 2013;45:180-5.

30. Brown LF et al. Expression of Tie1, Tie2, and angiopoietins 1, 2, and 4 in Kaposi's sarcoma and cutaneous angiosarcoma. Am J Pathol. 2000;156(6):2179–83.

31. Hirakawa N et al. Overexpression of bcl-2 protein in synovial sarcoma: a comparative study of other soft tissue spindle cell sarcomas and an additional analysis by fluorescence in situ hybridization. Hum Pathol. 1996;27:1060–5.

32. Charytonowicz E et al. PAX7-FKHR fusion gene inhibits myogenic differentiation via NF-kappaB upregulation. Clin Transl Oncol. 2012;14:197–206.

33. van Gaal JC et al. Anaplastic lymphoma kinase aberrations in rhabdomyosarcoma: clinical and prognostic implications. J Clin Oncol. 2012;30(3):308-15.

34. Boone P et al. Simultaneous autophagy induction and inhibition induces cell death through necroptosis in sarcomas that lack argininosuccinate synthetase 1 expression. Presented at the 17th Annual CTOS. Prague, Czech Republic. 14–17 November, 2012.


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YOGA AS TREATMENT FOR INSOMNIA AMONG CANCER PATIENTS AND SURVIVORS: A SYSTEMATIC REVIEW

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ABSTRACT

Between 15-90% of cancer patients and survivors report some form of insomnia or sleep quality impairment during and post-treatment, such as excessive daytime napping, difficulty falling asleep, difficulty staying asleep, and waking up too early. Insomnia and sleep quality impairment are among the most prevalent and distressing problems reported by cancer patients and survivors, and can be severe enough to increase cancer mortality. Despite the ubiquity of insomnia and sleep quality impairment, they are under-diagnosed and under-treated in cancer patients and survivors. When sleep problems are present, providers and patients are often hesitant to prescribe or take pharmaceuticals for sleep problems due to polypharmacy concerns, and cognitive behavioural therapy for insomnia can be very difficult and impractical for patients to adhere to throughout the cancer experience. Research suggests yoga is a well-tolerated exercise intervention with promising evidence for its efficacy in improving insomnia and sleep quality impairment among survivors. This article provides a systematic review of existing clinical research on the effectiveness of yoga for treating insomnia and sleep quality impairment among cancer patients and survivors.

Keywords: Yoga, sleep, insomnia, cancer, survivorship, exercise.

INTRODUCTION

Between 15-90% of cancer patients and survivors report some form of sleep quality impairment both during and post-treatment, such as excessive daytime napping, difficulty falling asleep, difficulty staying asleep, and waking up too early.[1-10] These sleep quality impairments are also symptoms of insomnia, which is defined by one or more of these symptoms (e.g., difficulty falling asleep or difficulty staying asleep) in severe and persistent forms (3 or more days per week for one month or longer).[11] Insomnia and sleep quality impairment are among the most prevalent and distressing problems reported by cancer patients and survivors, and can increase the risk of cancer-related fatigue and depression, impair cancer-treatment adherence, physical function and quality of life, and, when severe, increase cancer mortality.[1-10,12,13] Despite the ubiquity of insomnia and sleep quality impairment, they are under-diagnosed and under-treated in cancer patients and survivors.[1-10,12,14]

Treatment options for insomnia and sleep quality impairment include: 1) pharmaceuticals, which do not cure insomnia and can lead to toxicities, negative interactions with cancer therapeutics, dependency, and rebound impairment after discontinuation; 2) traditional exercise, which is recommended in treatment guidelines, but not widely implemented in survivorship care plans beyond the use of generalised statements, in which survivors are encouraged to be physically active and exercise; and 3) psychobehavioural interventions.[1-10,13] Yoga is a well-tolerated exercise intervention with promising evidence for its efficacy in improving insomnia and sleep quality impairment among survivors.

YOGA

A Holistic Mind-Body Mode of Exercise

Yoga is an increasingly popular mind-body practice and is also characterised as a mindfulness mode of exercise.[15-18] There are many different styles and types of yoga. These are based on Eastern traditions from India (e.g. Classical, Advaita Vedanta, Tantra), Tibet (e.g. Tibetan), and China (e.g. Chi Kung, Tai Chi).[15,19,20] The word yoga is derived from its Sanskrit root 'yuj' which literally means 'to yoke' or join together. In this case, yoga refers to joining the mind and the body.[15,19,20] The earliest forms of yoga were firmly rooted in physical and mindful (breathing and meditative) practices and led to what is known today as classical yoga which forms the basis for most of the yoga currently taught today.[19] Hatha yoga, the foundation of all yoga styles and the most popular form, includes both Gentle Hatha and Restorative yoga, and is growing in acceptance for therapeutic use in traditional Western medicine.[13,15-18,21-24] Gentle Hatha yoga focuses on physical aspects and is part of many styles of yoga, including Iyengar, Anusara, and others.[15-18,21] Restorative yoga focuses on full relaxation and is part of the Iyengar style.[25,26] The combination of Gentle Hatha and Restorative yoga may provide an effective approach for improving sleep because it utilises a holistic sequence of meditative, breathing, and physical alignment exercises, requiring both the active and passive engagement of skeletal muscles.[15,16,21,22,25,26] Existing scientific evidence suggests that yoga is effective for improving insomnia and sleep quality impairment in cancer patients and survivors.[13,20,27-36]

EXISTING SCIENTIFIC EVIDENCE

Yoga for the Treatment of Insomnia and Sleep Quality Impairment

Research suggests that yoga is helpful in treating depression, anxiety, fatigue and other conditions associated with sleep disorders among healthy individuals and those with cancer.[37-39] Herein, we review the extant literature on yoga and its use in the treatment of sleep problems among cancer patients (Table 1).

Yoga Programme Evaluations

Four evaluations of community yoga programmes for cancer patients and survivors suggest that yoga may improve insomnia and sleep quality impairment.[40-43] For example, Joseph et al.[40] conducted an early study comparing yoga, support therapy, and meditation interventions among cancer survivors undergoing radiation therapy where participants in the yoga group reported improvements in sleep, treatment tolerance, mood, appetite, and quality of life. These yoga programmes were based in cancer centres or community-based yoga studios, and offered yoga classes specifically for cancer patients receiving treatment and survivors who had completed at least primary treatments. The yoga classes included a wide variety of postures and mindfulness exercises from different styles and types, and they were offered 1-2 times a week for 60-90 minutes. Participants in two of these programmes also attributed improvements in strength, physical function, and physical fitness to their yoga practice.[42,43] However, these reports utilised convenience samples and did not use rigorous research methods designed to answer specific scientific questions about the effects of yoga on sleep quality impairment. These programmes also did not use standardised yoga interventions that can be accurately and consistently replicated for dissemination and explicitly prescribed for the treatment of insomnia or sleep quality impairment. Finally, all of these studies used only patient-reports of insomnia or sleep quality impairment, some of which have not undergone rigorous validation, and no objective assessments of sleep such as polysomnography or actigraphy.

Phase I and II Pilot Clinical Trials

Although limitations exist (see Limitations of Existing Scientific Data on Yoga and Sleep section to follow), one Phase I and seven Phase II studies provide preliminary support for the safety, feasibility and efficacy of yoga for improving insomnia and sleep quality impairment among cancer patients and survivors.[20,25,27-30,34-36] Cohen et al.[20] published the first study investigating yoga and sleep using a validated measure of sleep quality impairment with defined clinical cut-offs (i.e., Pittsburg Sleep Quality Index) among survivors' post-adjuvant treatment. These studies assessed a range of yoga doses from 1-5 sessions/week with classes lasting 50-120 minutes using a variety of different styles and types of yoga over 4-26 weeks. The interventions included a variety of postures and mindfulness exercises.

Table 1. Published Phase I–III clinical research trials investigating the efficacy of yoga for treating insomnia and sleep quality impairment.

Phase I	Trial Design	Sample	Treatment Status	Type of Yoga	Dose Information	Outcomes
Ulger O et al., 2010[29]	1-arm	Breast Cancer (N=20)	Post-adjuvant treatment	Classical	Frequency: 2x/week Duration: 60 min/session 4 weeks Intensity: low to moderate	Sleep * ↑ Measure(s): Turkish version of Nottingham Health Profile
Phase II	**Trial Design**	**Sample**	**Treatment Status**	**Type of Yoga**	**Dose Information**	**Outcomes**
Cohen L et al., 2004[20]	2-arm RCT w/ SC waitlist	Lymphoma (N=39)	Mixed receiving active treatment and within 12 months post-adjuvant treatment	Tibetan	Frequency: 1x/week Duration: NA min/session 7 weeks Intensity: low	Sleep * ↑ Sleep meds* ↑ Measure(s): Pittsburgh Sleep Quality Index
Danhauer SC et al., 2009[25]	2-arm RCT w/ SC waitlist	Breast Cancer (N=44)	Mixed receiving active treatment and within 2 to 24 months post-adjuvant treatment	Integral (restorative yoga postures)	Frequency: 1x/week Duration: 75 min/session 10 weeks Intensity: low	Sleep * ↑ Measure(s): Pittsburgh Sleep Quality Index
Carson JW et al., 2009[28]	2-arm RCT w/ SC waitlist	Breast Cancer (N=37)	Post-adjuvant treatment	Yoga of awareness	Frequency: 1x/week Duration: 120 min/session 8 weeks Intensity: low to moderate	Sleep * ↑ Measure(s): Daily diary sleep rating
Vadiraja SH et al., 2009[30]	2-arm RCT w/ SC + support therapy	Breast Cancer (N=88)	During adjuvant radiotherapy	Integrated	Frequency: 3x/week Duration: 50 min/session 6 weeks Intensity: low to moderate	Sleep * ↑ Measure(s): European Organisation for Research in the Treatment of Cancer QOL C30

Phase I	Trial Design	Sample	Treatment Status	Type of Yoga	Dose Information	Outcomes
Chandwani KD et al., 2010[34]	2-arm RCT w/ SC waitlist	Breast Cancer (N=61)	During adjuvant radiotherapy	Patanjali from VYASA	Frequency: 2x/week Duration: 60 min/session 6 weeks Intensity: low to moderate	Sleep **NC** Measure(s): Pittsburgh Sleep Quality Index
Bower JE et al., 2012[27]	2-arm RCT w/ SC + health education	Breast Cancer (N=31)	Survivors post-adjuvant treatment	Iyengar	Frequency: 2x/week Duration: 90 min/session 12 weeks Intensity: low to moderate	Sleep **NC** Measure(s): Pittsburgh Sleep Quality Index
Dhruva A et al., 2012[36]	2-arm RCT w/ SC waitlist	Mixed types of Cancer (N=23)	Receiving intravenous chemotherapy	Pranayama	Frequency: 1x/week Duration: 60 min/session 12 months Intensity: low	Sleep * ↑ Measure(s): General Sleep Disturbance Scale
Cadmus-Bertram L et al., 2013[35]	2-arm BRCT w/ SC waitlist	Breast Cancer (N=32)	Post-adjuvant treatment	Viniyoga	Frequency: 5x/week Duration: 75 min/session 6 months Intensity: low to moderate	Sleep **NC** Measure(s): Pittsburg Sleep Quality Index
Phase III	**Trial Design**	**Sample**	**Treatment Status**	**Type of Yoga**	**Dose Information**	**Outcomes**
Mustian KM et al., 2010[32]	2-arm RCT w/ SC waitlist	Mixed Cancer Survivors (N=410)	Survivors post-adjuvant treatment	YOCAS®	Frequency: 2x/week Duration: 75 min/session 4 weeks Intensity: low to moderate	Sleep * ↑ Sleep meds* ↑ Measure(s): Pittsburg Sleep Quality Index & Actigraphy

RCT: randomised, controlled trial; BRCT: block-randomised, controlled trial; NC: no change; SC: standard care; HE: health education; NA: not available in published article.

The interventions were deemed safe and feasible for cancer patients receiving treatment and for survivors. Participants enjoyed the yoga interventions and in five studies reported improvements in insomnia and sleep quality impairment; three studies showed no changes in insomnia or sleep quality impairment.[27,34,35] Bower et al.[27] published the first study testing the efficacy of yoga for treating sleep problems that both blinded participants to the study hypotheses and used a rigorous time and attention control condition. Six of the Phase II randomised controlled trials (RCTs) compared yoga to a waitlist control, one to a support therapy control condition and one to a health education control condition.[27,30] The latter two studies suggest that yoga may be more effective for improving insomnia and sleep quality impairment than counselling, health education, time and attention.

Phase III Randomised Controlled Clinical Trials

Recently, Mustian et al.[13] published the first and only multicentre, Phase III, RCT trial examining the effects of yoga on insomnia and sleep quality impairment, assessed both via validated patient-report measures and objective actigraphy measures. This clinical trial is the most definitive trial to date, and demonstrates that yoga is effective for improving insomnia and sleep quality impairment when compared to a usual care waitlist control condition.[13] The trial compared a standardised yoga intervention (YOCAS®: 4 weeks, two times a week, 75 minutes/session; Gentle Hatha and Restorative Yoga) to a usual care waitlist control condition among 410 cancer survivors from 12 community oncology practices throughout the United States. Participants in the yoga condition demonstrated significant moderate-to-large improvements in patient-reported outcomes of insomnia and sleep quality impairment as well as significant improvements on objective actigraphy assessments of sleep outcomes, including wake after sleep onset and sleep efficiency. Yoga participants also significantly decreased their sleep medication use by 21%, while control participants increased their sleep medication use by 5%. Adherence to YOCAS® was good at 80%, and there were no study-related adverse events. All (100%) participants found the YOCAS® programme useful and would recommend it to other cancer survivors experiencing sleep problems.[13] Although positive, results are not generalisable to all types of yoga (e.g. yoga in a heated room, vigorous aerobic yoga), the majority of participants were women, white, and well-educated, and there were no long-term follow-ups to determine if the benefits of yoga on sleep lasted beyond the immediate post-intervention period.

LIMITATIONS OF EXISTING SCIENTIFIC DATA

While very promising, this body of scientific literature needs to be interpreted with caution due to design limitations. None of the Phase I-II studies were a definitive Phase III RCT that was planned and powered a priori to test the effects of yoga on insomnia or sleep quality impairment as a primary outcome. Many studies did not use validated patient reports of insomnia or sleep quality impairment, or objective assessments of sleep problems. The sample sizes were small, ranging from 20-88. They did not screen for or require a specific level of insomnia or sleep quality impairment as part of participant eligibility. The studies did not blind participants with the exception of the Bower study.[27] Yoga interventions were not standardised and were highly variable in content, type, intensity and duration of yoga, making it impossible to determine the actual dose of yoga needed to improve insomnia or sleep quality impairment. The yoga interventions were not described in great detail, making repeatability and standardised dissemination impossible. While general comments suggested the interventions were safe and that participants enjoyed them, no specific details were provided on the rate of adverse events. Information on participant attendance, compliance and attrition, details of the prescribed yoga dose versus the actual dose achieved (e.g. mode, frequency, intensity, duration), and information on sustainability of improvements in sleep quality impairment stemming from yoga were limited.

The Phase III clinical trial addressed many of the limitations of the Phase I-II clinical trials. For example, the Phase III trial was appropriately a priori designed and powered to test sleep as the primary outcome with a sample of 410 survivors, screened for a pre-defined baseline level of sleep quality impairment, used validated patient report and objective measures of sleep, rigorously standardised the yoga intervention, and checked for intervention quality, fidelity and

drift. The yoga prescription in the intervention was fully detailed in the publication along with accurate reporting of adverse events, attendance, compliance, and attrition, as well as the achieved dose of yoga versus the prescribed dose of yoga. To date, we could find no studies that have compared yoga to a gold-standard treatment for insomnia or sleep quality impairment, such as pharmaceuticals or cognitive behavioral therapy for insomnia — a required next step in clinical research if yoga is to be considered as such a treatment. In addition, no studies examined the individual components of yoga (i.e. physical postures, breathing and mindfulness activities) to determine which single component, if any, is primarily responsible for the positive effects stemming from yoga or any possible biological mechanisms (e.g. circadian, muscular, cardiovascular, pulmonary, neurological, immunological or neuroendocrine). Yoga may improve insomnia or sleep quality impairment, but an important body of knowledge needs to be developed in order to better tailor yoga prescriptions to improve sleep problems, and meet the unique needs of individual cancer patients and survivors. Finally, these studies include primarily Caucasian, well-educated, middle to upper-middle class women; they have very little racial, economic, social, cultural, gender or age diversity in the sample populations limiting external validity. Importantly, this limits the ability to determine which patient profile may be best suited for and have the best response to yoga therapy. For example, what about the impact of being male, having a cancer diagnosis other than breast cancer, or being non-white, socially isolated, or unemployed.

CLINICAL IMPLICATIONS

While yoga is increasingly popular throughout the world, and there are many books and DVDs as well as cancer centre and community programmes marketed toward cancer survivors (e.g. 'Gentle Yoga for Cancer Patients,' 'Yoga for Breast Cancer Patients and Survivors,' and 'Healing Yoga'), there is little, if any, scientific evidence as to the efficacy of these programmes for improving insomnia or sleep quality impairment among cancer survivors. These yoga programmes are not professionally regulated with respect to instructor qualifications and licensure, or adherence to best practice, standard of care or evidence-based therapeutic guidelines, resulting in significant variability as to what is offered to cancer patients and survivors. For example, some yoga programmes focus on very gentle, low-intensity, meditative practices (e.g. Restorative, Integral, Svaroopa), while others focus on vigorous practices (e.g. Power, Ashtanga), and yet others focus on both (e.g. Hatha, Iyengar, Kundalini).[44] Some programmes modify the yoga environment by using heaters and humidifiers (e.g. Bikram) or props such as straps, blocks, ropes and chairs (e.g. Iyengar).[44] Class structure varies considerably with some classes focusing only on physical postures and no mindfulness exercises, while others only include mindfulness exercises and no physical postures. The small number of studies examining the safety and effectiveness of only limited styles and types of yoga for improving insomnia and sleep quality impairment among survivors, coupled with the lack of regulation and wide variability of yoga offerings, substantially increases the chance that patients and survivors may spend a sizeable amount of time, energy and money participating in yoga programmes that may not be safe or effective. For example, yoga in a room heated to over 100 degrees Fahrenheit may be contraindicated for some survivors, and vigorous yoga may result in excessive muscle soreness and joint pain, increasing insomnia or sleep quality impairment. With this in mind, oncology practitioners can play an important role in helping cancer patients and survivors safely and effectively participate in yoga.

Despite their limitations, these Phase I-III studies collectively suggest that: 1) cancer patients and survivors can safely participate in yoga during and after cancer treatments; 2) yoga interventions are feasible in a variety of cancer centres and community-based yoga studios; 3) cancer patients and survivors participating in these yoga programmes enjoy them and find them beneficial; 4) participation in low-to-moderate intensity yoga that incorporates Gentle Hatha and Restorative postures, breathing and meditation exercises ranging from one-five sessions/week for 50-120 minutes per session over a period of 4-26 weeks may lead to improvements in insomnia and sleep quality impairment; and 5) participation in standardised yoga programmes designed explicitly for cancer patients and survivors experiencing sleep problems, such as YOCAS®, will reduce the insomnia and sleep quality impairment they experience.

Clinicians can provide important information to help cancer patients and survivors understand how they can safely begin or continue an exercise programme — in this specific case, yoga – during and after treatments.[45] Patients and survivors can benefit from knowing potential contraindications (e.g. orthopaedic, cardiopulmonary and oncologic) that might affect their exercise safety and tolerance.[46] Contraindications do not necessarily mean that a cancer patient or survivor cannot participate in yoga at all; in fact, this is rarely the case. In most instances, contraindications simply require specific modifications to the yoga regimen so that the individual can safely and effectively participate and achieve physical and mental health benefits. The American College of Sports Medicine (ACSM) Exercise Guidelines for Cancer Patients and Survivors — the only guidelines currently based on scientific evidence — provide an excellent resource regarding recommendations for screening and evaluation of cancer patients and survivors prior to participation in yoga (Tables 2 and 3).[46]

In addition, referral resources can help patients and survivors connect with the most qualified and competent yoga instructors in their community, particularly those who have special training and experience working with cancer patients and survivors, or individuals with other medical conditions. Patients and survivors with interest in yoga may also benefit from understanding that the styles and types of yoga that have been tested and been shown safe and effective for improving sleep among cancer patients and survivors include primarily, Gentle Hatha or Restorative postures combined with breathing and meditation exercises, and they are of low-to-moderate intensity. When screening patients and survivors for sleep problems and making clinical recommendations about the use of yoga for managing sleep problems, research suggests yoga is effective for individuals who reported mild-to-moderate sleep quality impairment as well as clinical insomnia, continue to report sleep problems after trying pharmaceutical treatments, demonstrate greater than 1 hour of wakefulness in the middle of the night, and have very poor sleep efficiency (60% or lower), or some combination

Table 2. Exercise guidelines for cancer patients and survivors adapted from the American College of Sports Medicine.[45,46]

Mode of Exercise	Recommendation
Aerobic Exercise	Achieve a weekly volume of 150 minutes of moderate intensity exercise or 75 minutes of vigorous intensity exercise, or some combination of the two.
Resistance Exercise	Perform strength training exercises 2-3 times per week. Include exercises that target all of the major muscle groups.
Flexibility Exercise	Include stretching exercises for all of the major muscle groups on all the days that other exercises are performed.
Additional Information	Return to normal activity as soon as possible during and following cancer treatment. Some exercise is better than none. Start slowly and progressively increase. Strive to achieve the recommended levels of exercise. See a medical professional if any questions or concerns arise. See an exercise oncology professional for assistance with exercise testing, prescription, and monitoring.

Table 3. Examples of exercise contraindications among cancer patients and survivors adapted from the American College of Sports Medicine.[45,46]

Examples of Cancer-Specific Concerns	Examples of Recommendations
Extreme fatigue, anaemia, and ataxia	Refer to medical specialist and exercise oncology professional to determine if exercise is safe. If determined to be safe, exercise at a low intensity, as tolerated, preferably under the supervision of an exercise oncology professional.
Surgery	Allow sufficient time to heal after surgery before commencing exercise.
Pain at surgery site	Refer to surgeon and/or physical therapist for clearance prior to exercise. Use exercises that do not involve that area of the body until pain is appropriately managed.
Limited mobility at surgery site	Refer to surgeon and/or physical therapist for clearance prior to exercise. Consider physical activity that does not involve that area of the body.
Risk of hernia due to ostomy	Avoid contact sports and exercises that increase intra-abdominal pressures.
Swelling and lymphoedema	Refer to oncologist and physical therapist for clearance prior to exercise. Monitor limb circumference and stop exercise and seek medical evaluation if circumference changes in patients/survivors. Patients at increased risk can wear a compression garment when exercising.
Peripheral neuropathy	Refer to neurologist, physical therapist and exercise oncology professional. Monitor closely for balance impairments. Include exercises that improve balance.
Cardiovascular toxicities	Refer to cardiologist and exercise oncology professional to determine if exercise is safe.
Compromised immune function	Refer to exercise oncology professional. Prescribe exercise at a low-to-moderate intensity. Ensure facility is clean to reduce infection risk.
Increased fracture risk	Avoid exercise that puts excessive stress on bones, including high impact activities.

of these characteristics. Patients and survivors with these characteristics were shown to derive the greatest benefits from participation in yoga — specifically, improved sleep with reduced medication use.

SUMMARY AND FUTURE RESEARCH DIRECTIONS

Although a definitive Phase III RCT has been published and positive results were noted from

this study and the other smaller Phase I-II studies preceding it, the variability across studies and methodological limitations in the published literature continue to limit the extent to which yoga can be considered effective for treating insomnia or sleep quality impairment among cancer patients and survivors. Further research is needed to determine whether yoga is equivalent or superior to existing gold standard pharmaceutical and cognitive behavioral treatments for insomnia and sleep quality impairment. Studies need to employ validated gold-standard patient reported outcomes of insomnia and sleep quality impairment along with objective measures of insomnia and sleep quality impairment. Studies also need to conduct long-term follow-up assessments (e.g., 3, 6, 9, 12 months post intervention) to determine the duration and magnitude of any sleep benefits derived from yoga. In addition, a wider variety of yoga types and intensities need to be examined for their safety and efficacy in treating sleep problems among cancer patients and survivors. Dismantling trials are needed to determine which component of yoga (e.g. postures, breathing or meditation) is primarily responsible for its effectiveness, along with mechanistic studies to determine the biopsychosocial pathways through which yoga exerts a positive influence on sleep and other toxicities related to cancer and its treatments, such as fatigue, functional decline, cognitive impairment, and deregulated immune function, among others. Trials are needed to elucidate effective ways to increase yoga participation among racially, economically, socially and culturally diverse patients and survivors, as well as older and male cancer patients and survivors. Trials are needed to determine which patients and survivors are most likely to benefit from yoga as a treatment for sleep problems. Trials are also needed to compare the efficacy of yoga to other modes of exercise, such as walking and resistance training, for improving sleep. Finally, trials are needed that extend yoga to the cancer patients' and survivors' care partners (e.g. sister, brother, mother, father, child, spouse, or friend), who provide unpaid care and support to the patient at significant expense to their own health throughout the cancer experience, and without whom effective treatment, support and recovery would not be possible for these patients — these trials may show yoga to be a low-cost and effective therapeutic intervention for both patient and care partner in dyads — with even greater benefits to the patient or survivor than when interventions are directed solely at the individual.

REFERENCES

1. Ancoli-Israel S. Recognition and treatment of sleep disturbances in cancer. J Clin Oncol. 2009;27:5864-6.

2. Savard J et al. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol. 2011;29:3580-6.

3. Palesh OG et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol. 2010;28:292-8.

4. Berger AM et al. Values of sleep/wake, activity/rest, circadian rhythms, and fatigue prior to adjuvant breast cancer chemotherapy. J Pain Symptom Manage. 2007;33:398-409.

5. Ancoli-Israel S et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer. 2006;14:201-9.

6. Savard J et al. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep. 2001;24:583-90.

7. Schultz PN et al. Breast cancer: relationship between menopausal symptoms, physiologic health effects of cancer treatment and physical constraints on quality of life in long-term survivors. J Clin Nurs. 2005;14:204-11.

8. Berger AM et al. Fatigue and other variables during adjuvant chemotherapy for colon and rectal cancer. Oncol Nurs Forum. 2010;37:E359-69.

9. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol. 2001;19:895-908.

10. Pinto AC, de Azambuja E. Improving quality of life after breast cancer: dealing with symptoms. Maturitas. 2011;70:343-8.

11. Palesh O et al. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. Nat Sci Sleep. 2012;4:151-62.

12. Partinen M HC. Epidemiology of sleep disorders. Philadelphia: Elsevier; 2005.

13. Mustian KM et al. Multicenter, Randomized Controlled Trial of Yoga for Sleep Quality Among Cancer Survivors. J Clin Oncol. 2013;26:3233-41.

14. Palesh O et al. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. Nat Sci Sleep. 2012;4:151-62.

15. Bower JE et al. Yoga for Cancer Patients and Survivors. Cancer Control. 2005;12:165-71.

16. Elkins G et al. Mind-body therapies in integrative oncology. Curr Treat Options Oncol. 2010;11:128-40.

17. Mustian KM et al. Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. The Oncologist. 2007;12:52-67.

18. Mustian KM et al. Exercise for the management of side effects and quality of life among cancer survivors. Curr Sports Med Rep. 2009;8:325-30.

19. Kirk M, Boon B. Hatha Yoga for greater strength, flexibility, and focus. Champaign, IL: Human Kinetics; 2003.

20. Cohen L et al. Psychological adjustment

and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. Cancer. 2004;100:2253-60.

21. Saper RB et al. Prevalence and patterns of adult yoga use in the United States: results of a national survey.[comment]. Altern Ther Health Med. 2004;10:44-9.

22. Smith KB, Pukall CF. An evidence-based review of yoga as a complementary intervention for patients with cancer. Psycho-oncology. 2009;18:465-75.

23. Muktibodhananda S. Hatha Yoga Pradipika. Poughkeepsie, NY: Nesma Books India; 2000.

24. Lasater J. Relax and Renew Restful Yoga for Stressful Times. Berkeley, CA: Publishers Group West; 1995.

25. Danhauer SC et al. Restorative yoga for women with breast cancer: findings from a randomized pilot study. Psycho-oncology. 2009;18:360-8.

26. Danhauer SC et al. Restorative yoga for women with ovarian or breast cancer: findings from a pilot study. J Soc Integr Oncol. 2008;6:47-58.

27. Bower JE et al. Yoga for persistent fatigue in breast cancer survivors: A randomized controlled trial. Cancer. 2012;118:3766-75.

28. Carson JW et al. Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. Support Care Cancer. 2009;17:1301-9.

29. Ulger O, Yagli NV. Effects of yoga on the quality of life in cancer patients. Complement Ther Clin Pract. 2010;16:60-3.

30. Vadiraja SH et al. Effects of yoga on symptom management in breast cancer patients: A randomized controlled trial. Int J Yoga. 2009;2:73-9.

31. Mustian KM et al. YOCAS® Yoga significantly improves circadian rhythm, anxiety, mood and sleep: A randomized, controlled clinical trial among 410 cancer survivors. Support Care Cancer. 2011;19:317-8.

32. Mustian KM et al. Effect of YOCAS® yoga on sleep, fatigue, and quality of life: A URCC CCOP randomized, controlled clinical trial among 410 cancer survivors. J Clin Oncol. 2010;28:639.

33. Mustian KM et al. YOCAS® Yoga improves insomnia among 410 cancer survivors. Int J Behavioral Medicine. 2010;17:209.

34. Chandwani KD et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. J Soc Integr Oncol. 2010;8:43-55.

35. Cadmus-Bertram L et al. Predictors of adherence to a 26-Week viniyoga intervention among post-treatment breast cancer survivors. J Altern Complement Med. 2013;19:751-8.

36. Dhruva A et al. Yoga breathing for cancer chemotherapy-associated symptoms and quality of life: results of a pilot randomized controlled trial. J Altern Complement Med. 2012;18:473-9.

37. Balasubramaniam M et al. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Front Psychiatry. 2012;3:117.

38. Buffart LM et al. Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC Cancer. 2012;12:559.

39. Cramer H et al. Yoga for depression: a systematic review and meta-analysis. Depress Anxiety. 2013;30:1068-83.

40. Joseph CD. Psychological supportive therapy for cancer patients. Ind J Cancer. 1983;20:268-70.

41. Rosenbaum E et al. Cancer supportive care, improving the quality of life for cancer patients. A program evaluation report. Support Care Cancer. 2004;12:293-301.

42. Duncan MD et al. Impact and outcomes of an Iyengar yoga program in a cancer centre. Curr Oncol. 2008;15Suppl2:s109 es72-8.

43. Speed-Andrews AE et al. Pilot evaluation of Iyengar yoga program for breast cancer survivors. Cancer Nursing. 2010;33:369-81.

44. Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. J Altern Complement Med. 2010;16:3-12.

45. Mustian KM et al. Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction: a review. Oncol Hematol Rev. 2012;8:81-8.

46. Schmitz KH et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42:1409-26.

Innovative organ creation:
Another step to curing tumours?

A THREE-DIMENSIONAL bioengineered/computational model, created by the Keck School of Medicine of the University of Southern California (USC), could reveal clues to metastatic cancer growth. This is the first-ever bioengineered liver 'organoid' and could mark the beginning of discoveries into different angles of attack on tumour growth in cancers.

The $2.3 million project, named 'An Integrative Computational and Bioengineered Tissue Model of Metastasis' will be supervised by Prof David Agus, Director of the USC Centre for Applied Molecular Medicine.

"Studying cancer metastasis in the lab is problematic because of discrepancies between cell culture models and tumour growth in living organisms," Prof Agus stated. "Our research merges the methods of physical science, regenerative medicine and tissue engineering to create a tissue model that approximates the actual environment tumours live."

The project will involve several stages; the first concerns calibrating the model with data from the bioengineered liver tissue. The second will then require simulating physical changes to the growing tumours which would affect it in the human body, such as alterations to oxygenation and drug treatment. Then finally, comparisons will be made between the simulated tumour growths in real patients with outcome data from these patients.

> "Studying cancer metastasis in the lab is problematic because of discrepancies between cell culture models and tumour growth in living organisms."
>
> *Prof David Agus*
> *Director, USC Centre for Applied Molecular Medicine*

This model is the winner of the 'Provocative Questions' grant awarded by the National Cancer Institute (NCI). Launched in 2012, the NCI grant project is based on 20 imperative questions introduced by the research community, and was proposed to encourage cancer researchers to search for imaginative, effective ways to study cancer.

Cancer costs multi-billions to EU

"We also need to understand why the UK's cancer mortality rates remain higher than many EU countries despite a similar spend on cancer care."

Sara Osborne
Head of Policy, Cancer Research UK

THE ECONOMIC impact of cancer within the European Union (EU) amounts to €126 billion (£107 billion) a year, according to a Europe-wide analysis.

The study analysed data from 27 EU nations in 2009. The researchers found that Germany, Luxembourg, France, Italy, and the United Kingdom, accounted for more than two-thirds of the total cost, resulting in €83 billion (£70 billion) between them.

Dr Ramon Luengo-Fernandes, from the Health Economics Research Centre at the University of Oxford, UK, said: "By estimating the economic burden of several diseases it will be possible to help allocate public research funding towards the diseases with the highest burden and highest expected returns for that investment."

The loss of productivity, a result of work missed due to sickness or death, cost €52 billion (£44 billion), healthcare costs including drugs and also doctors' time, amounted to €51 billion (£43 billion), while €23 billion (£19.5 billion) was spent on care provided by family and relatives.

Sara Osborne, the Head of Policy at Cancer Research UK, said: "This study reinforces why research is vital to improve our understanding of the causes of cancer – so that we lessen the impact of the disease and develop better ways to prevent and treat the illness.

"We also need to understand why the UK's cancer mortality rates remain higher than many EU countries despite a similar spend on cancer care."

Results revealed that lung cancer has the highest overall cost, whereas breast cancer remained the highest for healthcare costs, mostly due to cost of the drugs needed to fight the disease.

Results such as these are useful in order to ensure that decision-makers across the EU identify key areas where money needs to be invested. Although these figures for treating cancer are high, the economic burden was low compared to money spent on dementia and cardiovascular disease.

Internet connects cancer patients

CANCER sufferers can find the internet to be a rich source of information and news. It also offers a platform for patients to share their experiences, offer support, and discuss their needs. For many healthcare professionals, sources such as these may prove useful when gathering information on cancer patients.

Dr Kathleen Beusterien from Outcomes Research Strategies in Health, Washington DC, USA, and her colleagues examined the online narratives of patients who are undergoing chemotherapy for colorectal cancer. Their study highlighted experiences such as emotional wellbeing and the physiological consequences of side-effects.

The researchers used qualitative analysis to separate the discussions into areas such as physical side-effects, work productivity, and emotional impact. The information gathered was able to illustrate the real-world experiences of patients.

Their results – published in *ecancermedicalscience* – found that gastrointestinal problems, chemotherapy's most common side-effect, was most requently discussed, while the most common emotion expressed was hope.

This web-based analysis provides healthcare professionals with a valuable insight into the real-world experiences of cancer treatments on patients. Moreover, as the rise of personalised medicine and patient empowerment grows, social media can prove to be a very important and beneficial role.

Proton therapy: a more effective treatment for children

PROTON therapy may be an effective way of treating paediatric patients with sarcomas and brain tumours adjacent to the brainstem, rather than using radiation therapy.

In young patients, proton therapy offers an advantage: the brain is less exposed to radiation, and the therapy may also limit the dose to a child's hearing, hormone, and vision centres, adjacent to the tumour.

Prof Daniel J. Indelicato, Associate Professor in the University of Florida's Department of Radiation Oncology, Florida, USA, said: "This study provides important evidence that proton therapy may be safely delivered to our most vulnerable patients with challenging tumours."

The study, the largest of this type ever presented, assessed 313 children who received a high radiation dose to the region around the brainstem. Many of the children had tumours in the critical location near the base of their skull and spinal cord. The results highlighted that 90% of children who were treated at the UF Proton Therapy Institute since 2006 have survived beyond 2 years and the rate of serious side-effects involving the brainstem was 2%.

Prof Indelicato added: "Whenever a child experiences a side-effect from radiation that impacts the brainstem, it is a very serious and potentially life-threatening event.

"Across our entire discipline, regardless of the treatment modality, paediatric radiation oncologists need more information to identify patients at risk. This study contributes valuable radiation dose parameters to help guide the design of safe radiation treatment plans."

UK PM announces continuation of Cancer Drugs Fund until 2016

UK Prime Minister David Cameron has announced that his government will be investing an extra £400 million in the Cancer Drugs Fund (CDF). This will mean that thousands of cancer patients in the UK will now be able to receive life-extending drugs.

The CDF allows cancer patients faster access to drugs which would not routinely be available on the NHS but which the doctors believe are right for them. Dr Andrew Protheroe, a Consultant in Medical Oncology at The Churchill Hospital, Oxford, UK, said: "The more treatment options that are available to me, the better job I feel I can do for my patients. There is nothing more frustrating than knowing there is an effective, licensed, evidenced-based treatment available which I am not allowed to use. It is like trying to do your job with one hand tied behind your back."

More than 34,000 patients have benefited since the CDF's creation in 2010, with Cameron now confirming the continuation of the Fund until March 2016.

Cameron said: "When I became Prime Minister 3 years ago, many patients with rare cancers were being denied lifesaving treatments. This is why we created the Cancer Drugs Fund, it is why we are extending it, and it is why we are partnering with Cancer Research UK to conduct new research into the effectiveness of cancer drugs."

Cancer Research UK and the Government-owned Genomics England have partnered together in order to map the whole DNA code of 3,000 cancer patients, as well as a further 3,000 whole DNA sequences for their cancer tumours. The partnership looks to not only enable Britain to lead the world in unlocking the power of DNA data, but also to be the first country in the world to sequence 100,000 genomes, or individual DNA codes, within the next 5 years.

Continuity in primary care could accelerate cancer diagnosis

DELAYS in the diagnosis of cancer in primary care could be altered if there was a continuity of care, in which patients will see the same GP with whom they have built a relationship, according to data published in the *Journal of the Royal Society of Medicine*.

Late diagnosis of cancer is a leading cause in poor survival rates in the UK, and leads to over 157,000 deaths a year.

A team of primary care experts wrote that longer consultations and a better distribution of information to GPs, concerning referral pathways or new services, may have an impact on diagnosing cancer early, which will also have an impact on survival.

Dr Thomas Round, the lead author of the study, a Clinical Research Fellow at King's College London, UK, said: "Early diagnosis is the result of the best interaction between patients and their GPs. Some of the interventions we are suggesting, such as longer GP consultation times, have been advocated by the Royal College of General Practitioners, and could be implemented at an individual GP and practice level.

"However, they would be difficult to implement given recent NHS re-organisation and constrained budgets, with primary care dealing with 90% of NHS patient encounters with less than 9% of the NHS budget."

"Some of the interventions we are suggesting, such as longer GP consultation times, have been advocated by the Royal College of General Practitioners, and could be implemented at an individual GP and practice level."

Dr Thomas Round,
King's College London, UK

However, the authors have suggested that patients themselves may be a factor in delaying diagnosis as they may not respond or recognise warning symptoms. It has been suggested that if patients have access to information about themselves and access to decision making tools, this could lead to an increase in health literacy, improve accuracy in patient records, and encourage an adult-to-adult relationship which in itself improves health and outcomes.

The recent changes within the NHS and its limited resources may mean that these suggestions could be difficult to implement. However, they could improve early cancer diagnosis and survival, as well as providing a safe, productive, and rewarding working environment for GPs.

Is radiotherapy the way forward for bladder cancer patients?

RADIOTHERAPY could save bladder cancer patients from enduring surgery, according to results from the BC2001 radiotherapy study. Previously, in order to treat aggressive bladder cancer, the whole bladder would have been removed.

Removing the bladder in aggressive bladder cancer can cause many severe side-effects, often leaving the patient wearing a plastic bag to collect urine. The BC2001 study, which compared using radiotherapy on the whole bladder with targeted radiotherapy focused on the tumour, found these treatments effective.

Dr Robert Huddart, the lead investigator of the study at The Institute of Cancer Research, London, UK, said: "Our study was part of the largest ever clinical trial of radiotherapy in bladder cancer and shows that patients with the disease can be treated effectively with radiotherapy. With similar success rates to surgery and fewer side-effects whilst allowing patients to retain a functioning bladder, radiotherapy should be seen as an alternative to surgery."

Both treatments were able to prevent the tumour from returning in 60% of patients for at least 2 years. The survival rates, after a 5-year follow-up, were around 40% for both radiotherapy approaches. Moreover, these patients had a low-risk of severe side-effects. In patients whose tumours did return, it was not aggressive and only needed local treatment.

The Director of Clinical Research at Cancer Research UK, Kate Law, said: "Previous results from this trial changed how doctors treat bladder cancer, showing that giving patients chemotherapy and radiotherapy is better than radiotherapy alone."

"With similar success rates to surgery and fewer side-effects whilst allowing patients to retain a functioning bladder, radiotherapy should be seen as an alternative to surgery."

Dr Robert Huddary
The Institute of Cancer Research, London, UK

Blood pressure drug improves effects of chemotherapy

A DRUG which has been used for the last decade to treat blood pressure may also be able to improve the effects of chemotherapy.

The research was initially undertaken to discover the physical reasons as to why chemotherapy drugs might not be reaching their intended target. It also assessed whether losartan and other drugs could affect the forces within the tumours which compress and collapse blood vessels.

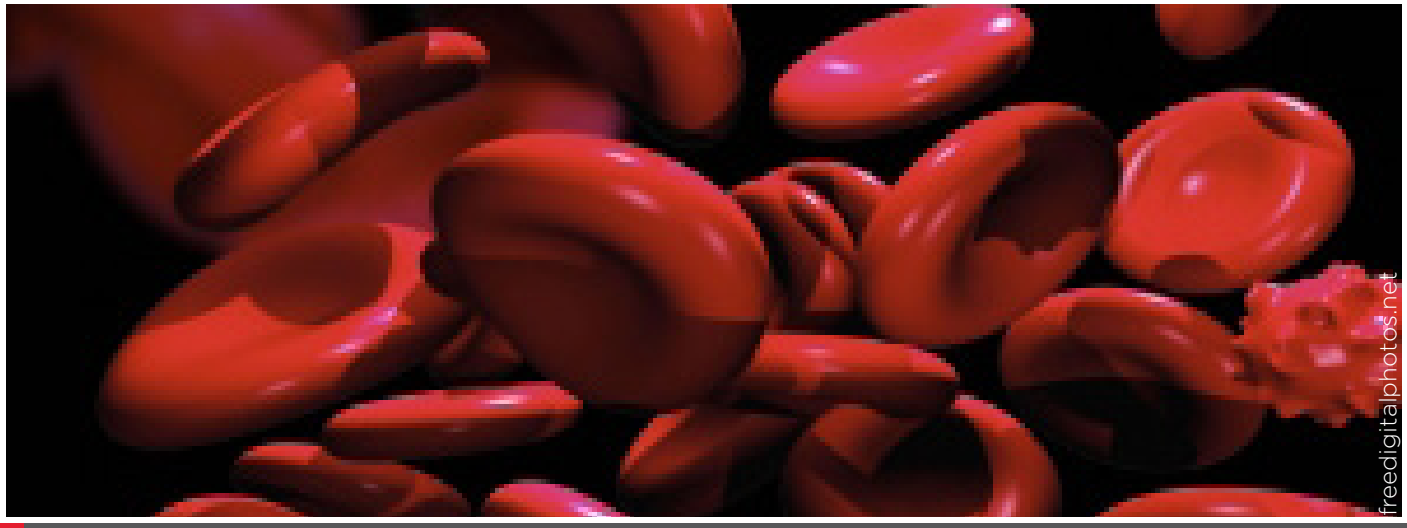
Dr Rakesh K. Jain, Director of the Steele Laboratory for Tumor Biology at Massachusetts General Hospital (MGH), USA said: "Unlike anti-angiogenesis drugs, which improve tumour blood flow by repairing the abnormal structure of tumour blood vessels, angiotensin inhibitors open up those vessels by releasing physical forces that are applied to tumour blood vessels when the gel-like matrix surrounding them expands with tumour growth."

In mice, the angiotensin-inhibitor drug losartan is able to open blood vessels in tumours and allow more chemotherapy to reach the cancer. Losartan was able to supress the activity of cancer-associated fibroblasts, inhibited the production of collagen and hyaluronan, and prevented the compression of blood vessels within tumours.

Dr Holger Gerhardt, a Cancer Research UK expert on blood vessel growth, said: "This important research helps explain why blood pressure drugs like losartan could help chemotherapy reach tumours, by stopping cells in the tumour matrix from producing certain molecules. This in turn reduces the tumour pressure and allows blood vessels to re-open and deliver the chemotherapy."

The results of the study found, in animal models, that the combination of losartan and chemotherapy delayed tumour growth and extended survival in mice with breast and pancreatic cancer.

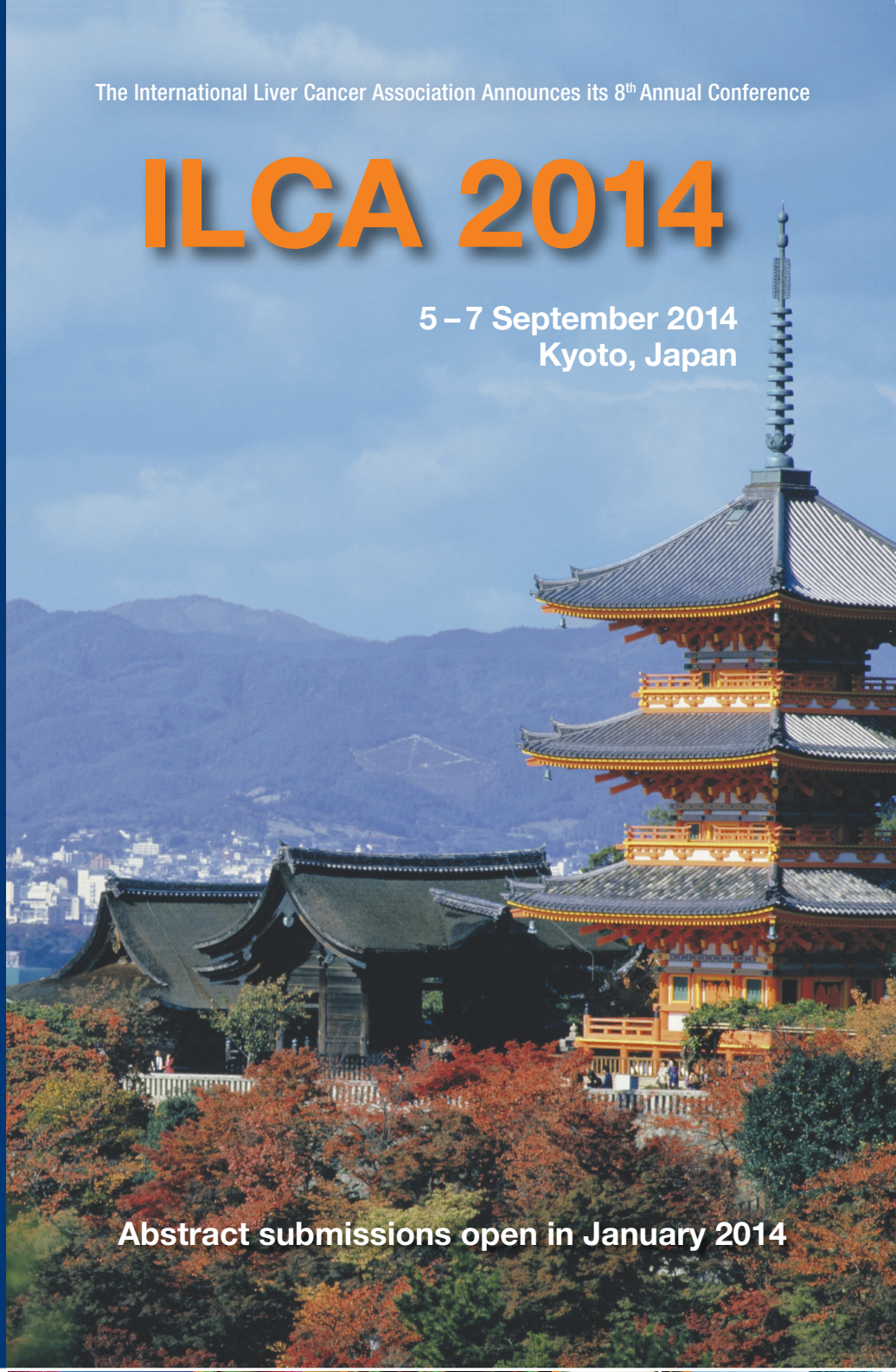
The MGH have now initiated clinical trials to test the effects of losartan in pancreatic cancer patients. These clinical trials will also be able to assess the efficiency and safety of the drug when combined with other types of cancer treatments.



The International Liver Cancer Association Announces its 8th Annual Conference

ILCA 2014

5 – 7 September 2014
Kyoto, Japan



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Conference highlights:

State-of-the-Art Lectures

Cutting Edge Symposia

General Sessions

Interactive Luncheon Workshops

e-Posters

Industry Exhibition

Networking Breaks and Reception

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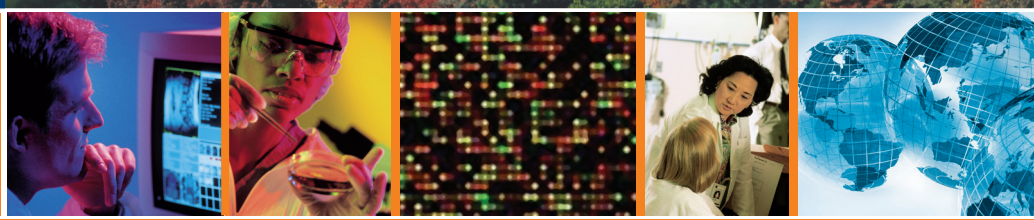
Abstract submissions open in January 2014

ILCA
International Liver Cancer Association



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Genomic Health is a molecular diagnostics company focused on the development and commercialisation of genomic-based clinical laboratory services that analyse the underlying biology of cancer, allowing physicians and patients to make individualised treatment decisions.

More than 19,000 physicians in over 70 countries have ordered around 335,000 Oncotype DX® tests for breast and colon cancer patients.

GSK Oncology is dedicated to pursuing innovation in cancer care to make a difference for patients, physicians, and communities. GSK pursues their pledge to engage and work with their communities, while striving to bring forth meaningful treatment choices.

Pfizer Oncology is committed to advancing the scientific understanding of cancer, and bringing new medicines to millions of cancer patients worldwide. Oncology itself is a research priority for Pfizer, with approximately 12% of the company's research and development investment devoted to discovering and developing innovative therapies for treating breast, colorectal, and other cancer.

PharmaMar is a Spanish company of the Zeltia Group, a leader in the development of anti-tumour drugs of marine origin. PharmaMar has carried out a pioneering programme in marine biotechnology, which has led to the discovery of new first-in-class drugs against cancer. PharmaMar currently has five products in clinical development.

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche's personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life, and survival of patients.

Varian Medical Systems, Inc. of Palo Alto, California, USA, the world's leading manufacturer of medical devices and software for treating cancer and other medical conditions with radiotherapy, radiosurgery, and brachytherapy.

The company supplies informatics software for managing comprehensive cancer clinics, radiotherapy centres, and medical oncology practices.

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Gastrointestinal Cancers Symposium

16th-18th Jan 2014

San Francisco, California, USA

This symposium, now in its 11th year, will bring together many disciplines, all of which focus on gastrointestinal cancers. It will address issues in areas such as prevention, screening, diagnosis, multidisciplinary treatment, and research, while focusing on such specific areas as the oesophagus, stomach, pancreas, colon, and rectum.

The 1st World Congress in Controversies in Multiple Myeloma (COMy)

23rd-25th Jan 2014

Bangkok, Thailand

This Congress will not only bring together top clinicians to debate vital issues in myeloma treatments, but will also address the most current challenging questions regarding both the clinical and therapeutic areas. In order to do this, the Congress brings to light the most recent data and information regarding multiple myeloma, ensuring that clinicians are provided with state-of-the-art recommendations regarding patient care.

The British Psychosocial Oncology Society (BPOS) 'The Emotional Impact of Cancer'

27th-28th Feb 2014

Preston, England

This 2-day meeting will provide a forum for professionals to meet. During this event, international speakers will present new findings and developments within the field of oncology, in anticipation that this new information will improve the quality of care delivered to patients.

Best of Oncology Conference

28th Feb 2014

Vancouver, British Columbia, Canada

This 1-day event will cover nine different tumour topics. During the conference, recent oncology trials and research findings will be discussed. It will also focus on the various controversies in the management of different cancers, and review the current standard of care for key malignancies.

13th ESO-ESMO Masterclass in Clinical Oncology

8th-13th Mar 2014

Ermatingen, Switzerland

This meeting is designed with clinical oncologists in mind, focusing on gastrointestinal, breast, genitourinary, gynaecological, head and neck, and lung cancers. There will be many clinical sessions which will concentrate on state-of-the-art clinical evaluations and treatments, referring to clinical guidelines.

ESTRO 33

4th-8th Apr 2014

Vienna, Austria

This event aims to address both the challenges radiation oncologists face today, and pre-empt the challenges which they will face in the future. Bringing together a multitude of oncologists, the meeting will evaluate the clinical treatment and primarily focus on treatments to improve patient care, including sessions on new technologies.

5th ESO-SIOP Europe Masterclass in Paediatric Oncology

17th-22nd May 2014

Ljubljana, Slovenia

This conference, which offers practiced-orientated training and teaching sessions, will be most beneficial to paediatric oncologists who wish to improve their skills in the clinical management of common childhood tumours. The session will focus on six tumours, including rare, bone, and central nervous system growths.

ESMO 2014 Congress

26th-30th Sept 2014

Madrid, Spain

The theme for ESMO 2014 is 'precision medicine in cancer care'. The Congress aims to provide a more personalised treatment approach, one that considers individual circumstances and the molecular characteristics. It hopes to bring together a range of oncologists who will work towards the common goal of providing improved patient outcomes.