ISSN 1751-4975

Oncology news

Volume 12 Issue 2 • May/June 2017 • www.oncologynews.biz

FREE SUBSCRIPTION

IN THIS ISSUE

Denys Wheatley
Editor.

Circadian Rhythm and Cancer

When I first heard about the possibility that circadian rhythms could affect cancer and its treatment, I was rather sceptical – would this make any significant difference to tumour behaviour? However, "normal" cells, especially those in tissues that are constantly turning over, seem to respond to changing levels of steroid hormones and other substances (e.g. melatonin and adrenaline) that fluctuate within each circadian cycle, and clearly cancer cells would also do so unless they have become independent of them. Loss of this temporal regulation may put cancer cells at a growth advantage. Since the cell cycle is affected by the daily rhythm, to what extent might more specific timing of treatments be used to improve the efficacy tumour therapy? It soon became apparent from the literature that "chronotherapy" has been going on for considerably longer than first thought [e.g. 1-3]*; indeed, it is now something of a cult. If the pace and volume of research continues, diurnal rhythms might well become important in some designing future treatment protocols.

The way metabolism changes diurnally will also affect how many drugs act, including anti-cancer agents. Our metabolic rate fluctuates considerably through 24 hours, largely depending on the level of mitochondrial activity. We know that many drugs are more effective if taken first thing in the morning, others at night. So the question is whether some anti-cancer treatments can be more effective if given at certain times, both on their own or after even more careful consideration where combination therapy is involved.

In combination therapy, it is often more effective to give one agent at a different time in relation to a second, i.e. sequentially rather than simultaneously. Where this is a relatively short interval, this may be where more attention should be given to the possible influence of circadian rhythm. It seems that even if two drugs or treatments are given simultaneously or close together, not a great deal of thought has often been given to the underlying cellular biology, which should be a guiding principle in choosing the optimal interval, for example see reference [4]. This interval might be a half a day, a day, a week or even longer depending on the responses of cells to the first intervention. As has already been shown [5], the first treatment can sometimes greatly weaken the growth of a tumour and cause regression, thereby providing a platform on which a second drug can administer the coup-de grace at a most appropriate time.

Even more pertinently, this sometimes means that the second agent can be given at a much lower dose than when administered alone, i.e. at a subclinical dose, substantially reducing side effects. Finding the optimal conditions and timings is difficult in clinical work because tumour cell behaviour during the course of treatment would need to be explored. However, the way that interplay between two drugs is tested experimentally is seldom comprehensive; a much more sophisticated programme is required, with escalating and de-escalating levels of each treatment in turn, and given at different intervals, possibly with a considerable break between the two. The permutations involved are huge; most studies have been little more than a first step towards optimisation, but there can be some short cuts, as I suggested in a previous editorial [6]. Building in the circadian rhythm as another factor will at the very least double the size of any comprehensive study. And we might have to consider at some time influences other than circadian rhythm that need to come into the equation (gravity, magnetic fields?).

REFERENCES

1. Chang L et al. *Research on radiotherapy at different times of the day for inoperable cervical cancer.* Int J Clin Pharmacol Ther. 2016;54:856-64.
2. Chan S et al. *Effects of circadian rhythms and treatment times on the response of radiotherapy for painful bone metastases.* Ann Palliat Med.2017;6:14-25.
3. Benedetto Grimaldi. *Lysosomotropic REV-ERB antagonism: A metabolic connection between circadian rhythm and autophagy may tell cancer cells "it's time to die".* Mol & Cell Oncology, 2015;2:2, e965626.
4. Fisi V et al. *Timed, sequential administration of paclitaxel improves its cytotoxic effectiveness in a cell cycle model.* Cell Cycle 2016;15:1227-33.
5. Cheng P N-M et al. *Pegylated recombinant human arginase (rhArg-peg5000mw) inhibits the in vitro and in vivo proliferation of human hepatocellular carcinoma through arginine depletion.* Cancer Res 2007;67:309-17.
6. Wheatley DN. *More on combinatorial therapy: possible stratagems.* Oncology News (Editorial) 2012;7:104.

Contents

Volume 12 Number 2 • May/June 2017

Erratum: It has been drawn to our attention that a diagram was accidently omitted from Dr Elisabetta Caspani's article in the March/April issue (2017; Vol 12: 11-12) "Are brain pericytes a new promising target to defeat Glioblastoma infiltration and recurrence?". The article has been corrected and has been reprinted in the Neuro-oncology supplement accompanying the May/June 2017 issue.

Cover picture: Debbie McGee is proud to provide her influential support for Brain Tumour Research and 'Wear A Hat Day' after she lost her beloved husband, Paul Daniels, to a brain tumour in 2016.

Oncology News is published by McDonnell Mackie,
88 Camderry Road, Dromore, Co Tyrone, BT78 3AT, N Ireland.

Publisher: Patricia McDonnell • Web: www.oncologynews.biz

Advertising and Editorial Manager: Patricia McDonnell
E: Patricia@oncologynews.biz
T/F: +44 (0)288 289 7023, M: +44 (0)7833 185116

Printed by: Warners Midlands PLC, T: +44 (0)1778 391057

https://is.gd/oncologynewsfb @OncologyNewsMag

British Neuro-Oncology Society

Dear Delegate

Imran Liaquat

The BNOS Conference seeks to rotate its conference themes and give the delegates the opportunity to be exposed to current 'hot topics'. This year's meeting programme has primarily been developed by the Local Organising Committee, which includes individuals from the fields of basic science, clinical care and quality of life. The aim of this meeting is to be all inclusive with regards to all forms of research from basic science through to quality of life that helps to advance the care of patients who have developed Brain tumours. Therefore the themes of this meeting can be divided into overlapping categories of basic science, clinical management and quality of life, which should appeal to a wide and diverse range of individuals from the Neuro-oncology diaspora. A very deliberate effort has been made to develop a programme that appeals to laboratory based researchers, clinicians, nursing staff and allied healthcare professionals. There are a number of parallel sessions that focus on basic science and quality of life topics, bridged by keynote invited plenary talks.

We have attracted a wide range of International invited expert speakers not only from within the UK but also from Europe, the US and Canada. The opening "Education Day" morning focuses on topical clinical issues in "Low Grade Gliomas", from imaging, through to WHO classification and Best clinical management. Professor Mark Bernstein, from Toronto will discuss Surgical decision making in Low Grade Glioma patients; Professor Jan Buckner, from the Mayo Clinic will focus on "Best Oncological Treatment in Low Grade Gliomas". In the afternoon there will be parallel sessions focusing on basic science and quality of Life/nursing issues. The science session will focus on stem cell and glioma biology, drug discovery, molecular therapeutics and immunotherapy. The quality of Life/nursing session will cover topics ranging from mood and cognitive disorders through to end of life care issues. The session will finish with an interactive mock multi-disciplinary meeting.

The body of the meeting follows a traditional format with alternating proffered paper sessions and invited lectures. The meeting proper starts on Thursday and the focus is on High Grade Glioma research in the morning, with the proffered lectures being delivered through parallel sessions followed by invited plenary talks from keynote speakers. The afternoon session will focus on Paediatric Oncology and Tumours in Young Adults and will follow a similar format to the morning session. The Friday morning session will focus on contemporary research in Cerebral Metastases and Clinical Trials.

A complimentary Welcome Reception will take place at Dynamic Earth, which is close to Holyrood Palace, the Scottish Parliament and Arthurs Seat. The Gala Dinner will take place at the Playfair Library on Thursday evening.

In addition to the programme there will be sponsored symposia on both the Wednesday and Thursday lunch time by Exhibitors.

We hope to see you in Edinburgh

Best Wishes,
Imran Liaquat,
Chair of the Local Organising Committee,
BNOS 2017 Edinburgh – Engaging Science Enhancing Survival

gliolan® 30 mg/ml powder for oral solution.
Qualitative and quantitative composition: One vial contains 1.17 g of 5 aminolevulinic acid (5-ALA), corresponding to 1.5 g 5 aminolevulinic acid hydrochloride (5 ALA HCl). One ml of reconstituted solution contains 23.4 mg of 5 aminolevulinic acid, corresponding to 30 mg 5 aminolevulinic acid hydrochloride (5 ALA HCl).
Therapeutic indications: gliolan is indicated in adult patients for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).
Posology and method of administration: This medicinal product should only be used by experienced neurosurgeons conversant with surgery of malignant glioma and in-depth knowledge of functional brain anatomy who have completed a training course in fluorescence-guided surgery. The recommended dose is 20 mg 5 ALA HCl per kilogram body weight.
Contraindications: Hypersensitivity to the active substance or porphyrins; acute or chronic types of porphyria; pregnancy.
Undesirable effects: Adverse reactions observed after the use for fluorescence-guided glioma resection are divided into the following two categories: Immediate reactions occurring after oral administration of the medicinal product before anaesthesia (= active substance-specific side effects); combined effects of 5 ALA, anaesthesia and tumour resection (= procedure-specific side effects).
Substance-specific side effects: *Uncommon:* Hypotension; nausea, photosensitivity reaction, photodermatosis.
Substance-specific side effects: *Uncommon:* Hypotension; nausea, photosensitivity reaction, photodermatosis.
Procedure-related side effects: The extent and frequency of procedure-related neurological side effects depend on the localisation of the brain tumour and the degree of resection of tumour tissue lying in eloquent brain areas. *Very common:* Anaemia, thrombocytopenia, leukocytosis. Blood bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase or blood amylase increased. *Common:* Neurological disorders (e.g. hemiparesis, aphasia, convulsions, hemianopsia). Thromboembolism. Vomiting, nausea. *Uncommon:* Brain oedema, hypotension. *Very rare:* Hypesthesia; diarrhoea. One case of moderate chills; one respiratory insufficiency after overdose, which resolved completely.
Legal classification: POM (prescription only medicine).
Price per vial: €980/ £ 950 ex. factory. **Marketing authorisation number:** EU/1/07/413/001-003.
Marketing authorisation holder: medac GmbH, Theaterstraße 6; D-22880 Wedel.
Date of revision of text: 02/2014.
gliolan has been authorised in all countries of the EU as well as in Iceland, Norway, Israel and Taiwan.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to medac drug safety at: drugsafety@medac.de

medac code: medacuk 021/04/2016
Date of Preparation: April 2016

Give her the best chance

medac

fluorescence-guided resection

Gliolan, for the visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV) in adult patients.

gliolan® seeing is the beginning

5-Amino Acid Fluorescence Guided Resections of High Grade Gliomas

Stephen J Price PhD FRCS(Neuro.Surg),
Consultant Neurosurgeon, Neurosurgery Division, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK.

Correspondence to:
E: sjp58@cam.ac.uk

High grade gliomas encompass a group of intrinsic and highly malignant primary brain tumours. Their inevitable local progression despite surgery and radiotherapy with concomitant and adjuvant chemotherapy contributes to their appalling prognosis. For an individual patient, brain tumours account for more average years of life lost than commoner cancers. The considered or perceived lack of new therapeutic options, and failure of trials of targeted therapies make it more important to optimise our existing treatments to develop marginal gains in outcome.

Surgery for glioblastomas

Surgery plays a key role in the management of high grade gliomas. The main aim is to provide representative tumour samples to allow histological and molecular characterisation of the tumour, but it also leads to the largest tumour cell kill of all available treatments that is independent on tumour genomics. But surgery alone cannot cure glioblastomas. Walter Dandy showed in the 1920s that even following hemispherectomy, patients lived longer but still died of progressive disease in the contralateral hemisphere.

Delaying progression is important in glioblastomas. As all current treatments fail to cure these tumours, our aim should be to provide good palliation – to keep the patient well with a good quality of life for as long as possible. Progression is usually marked by a deterioration in quality of life that never fully recovers with treatment.

It is now becoming clear that the extent of tumour resection is critical to survival. Although survival advantage has been reported after 78% of the contrast enhancing tumour is resected [1], complete resection of the enhancing tumour is associated with significantly improved survival [2]. A multi-centre observational study showed little differences in survival with either >0 to ≤1.5cm or >1.5cm enhancing residual tumour. Significantly prolonged survival was only seen where no contrast enhancing tumour is was left – the median survival of this cohort exceeded two years [3].

The real difficulty is achieving this maximal resection of contrast enhancing tumour. Identifying the tumour limits intra-operatively is difficult. When surgeons are were asked if they have had completely resected a glioblastoma, 70% felt they had, while early postoperative MRI showed that the actual complete resection rate was only 18%[4]. This is typical of other studies that suggest complete resection is only achieved in less than 30% of cases. There is therefore a great need to develop tools to allow maximal resection.

Principles of 5-Aminolevulinic Acid Fluorescence

Aminolevulinic acid hydrochloride (5-ALA) is an endogenous intermediate of the porphyrin biosynthesis pathway. It acts as a prodrug that is metabolised intracellularly to form the protoporphyrin IX (PPIX). In normal metabolic conditions the enzyme ferrochelatase catalyses the insertion of ferrous iron into PPIX to form protoheme. In many tumours, including glioblastomas, there is a deficiency of ferrochelatase and a reduction of ferrous iron leading to PPIX accumulation.

The exogenous application of 5-ALA leads to a highly selective accumulation of PPIX in tumour cells. PPIX is a fluorophore and absorption of light excites the PPIX molecules from their ground state. This effect is most efficient at wavelengths of approximately 400 nm (blue light). Decay from the excited state is accompanied by emission of red light (λmax = 635 nm) that can be visualised intraoperatively as pink fluorescence using specially modified operative microscopes. Bleaching of fluorescence does eventually occur as repeated excitation will lead to molecular breaks that prevent further fluorescence. Unlike other tumours, bleaching is not a major problem in glioma surgery as with every part of tumour resected, new tumour that has not been exposed to light [5].

Pre-clinical studies

Initial in vitro studies incubating C6 glioma cells with 5-ALA showed that PPIX accumulation and the associated fluorescence occurred. After 85 minutes of incubation no further increase in fluorescence occurred suggesting saturation of uptake with higher doses [6]. Injecting these cells into rats showed fluorescence only in regions of high density tumour, and was not seen in normal brain [6]. The peak fluorescence was seen 6 hours after dosing with 5-ALA [6]. Autoradiography studies show that disruption of the blood brain barrier is required to get sufficient 5-ALA into the brain to demonstrate fluorescence [7].

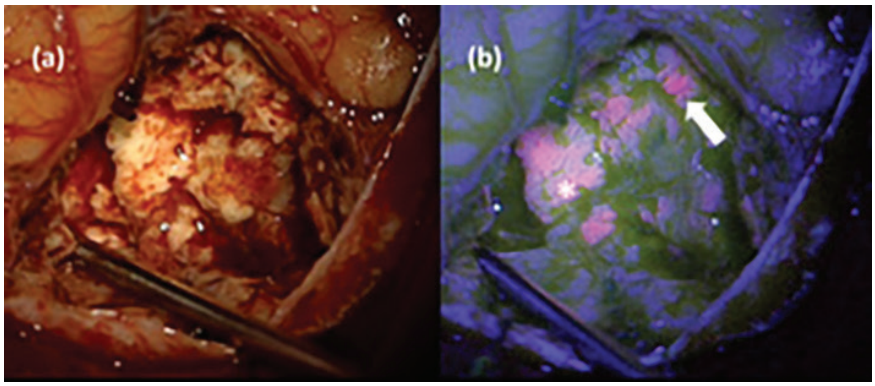


Figure 1: Intra-operative images during resection of a glioblastoma. (a) Shows the appearance under white light, and (b) under blue light. Under blue light areas of fluorescence can be clearly seen. Some areas (arrow) are strongly fluorescent. Other areas (*) are vaguely fluorescent.

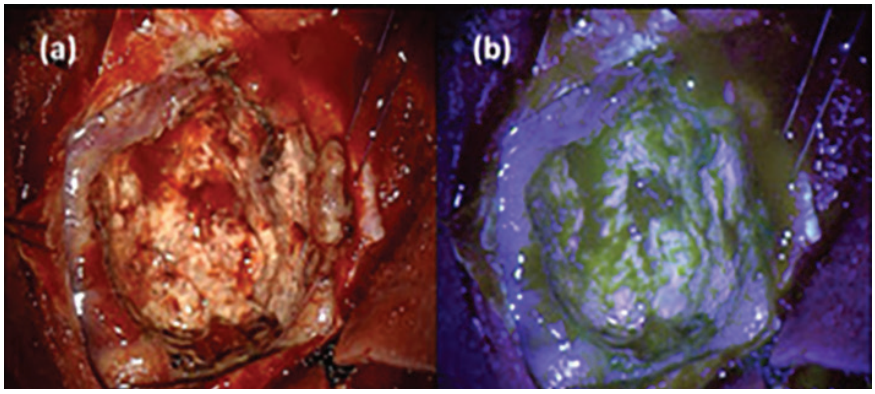


Figure 2: Images at the end of surgery under (a) white light and (b) blue light. There is no obvious residual fluorescence. This provides an objective end-point for surgery and is associated with high rates of complete resection of enhancing tumour.

Diagnostic accuracy of 5-ALA identifying high grade glioma

The selective production of PPIX in tumour cells but not normal brain cells provides an excellent way of identifying tumour intra-operatively (Figure 1). Studies looking at the diagnostic accuracy of 5-ALA show that it has a high positive predictive value (PPV) between 95%-100% [5,8-11] (see Table 1). The negative predictive value (i.e. no residual tumour in non-fluorescent tumour) is, however, relatively low with values between 40%-75% [5, 8-11]. This suggests 5-ALA can identify tumour with a high degree of accuracy, but can't detect all the tumour.

Initial studies in patients revealed there were different fluorescence intensities (Figure 1). Solid fluorescence was associated with high tumour cell density, vague fluorescence revealed infiltrating tumour cells [5,8]. The positive predictive value of these weakly fluorescent areas is 95% [11]. Histology of these vague fluorescent regions revealed features diagnostic of a GBM in only 8.2%, most specimens had features of hypercellularity and atypia (88.5%) [12].

In recurrent high grade gliomas, the diagnostic accuracy is lower. The positive predictive value is 96.6% [13]. Again, the intensity of fluorescence is important – the PPV of highly fluorescent tumour is 98.2% vs. vague fluorescent regions of 95.3%. This lower PPV is due to fluorescence in reactive astrocytes and macrophages and blood brain barrier leakage into normal brain [13].

The ability of 5-ALA at detecting high grade tumours has led to suggestions of other, unlicensed uses. One involves detecting anaplastic foci within lower grade tumours. One study found fluorescent regions in most anaplastic gliomas but failed to identify any in low grade tumours [14]. The second describes a method of using 5-ALA to ensure a positive diagnosis in stereotactic biopsy specimens. The sensitivity of 5-ALA for detecting high grade tumours is used to reduce the incidence of non-diagnostic biopsies and avoid complications from taking multiple biopsies [15].

Table 1: Summary of diagnostic accuracy from previous studies

Study	No. subjects	Positive predictive value	Negative predictive value
Stummer et al (1998)[5]	10	100%	75%
Stummer et al (2000)[8]	52	100%	50%
Diez Valle et al (2011)[10]	36	97%	66%
Roberts et al (2011)[9]	11	95%	40%
Stummer et al (2014)[11]	33	100%	40%

Table 2: Summary of rate of complete resection of tumours from literature

Study	No. of patients	% with complete resection of enhancing tumour
Stummer et al (2000)[8]	52	63%
Stummer et al (2006)[16]	270	65%
Feigl et al (2010)[17]	18	64%
Diez Valle et al (2011)[10]	36	83%
Schucht et al (2012)[18]	53	89%
Tykocki et al (2012)[19]	6	80%
Diez Valle et al (2014)[20]	131	67%

Improving Outcome with 5-ALA Guided-Resection

A common misconception is that 5-ALA will directly lead to an improvement in survival. 5-ALA's role is purely as a diagnostic aid – it has no anti-tumoural activity on its own. 5-ALA aims to identify tumour cells to improve the extent of resection, which in turn can improve progression free and overall survival.

The rate of complete resection of enhancing tumour was 63-89% using 5-ALA [8,10,16-20] (Table 2). This is far higher than the rate of less than 30% of patients previous studies have reported. The absence of fluorescence at the end of surgery provides an objective end-point to surgery (Figure 2), and predicts complete resection with a sensitivity of 76-100% [8,19,21].

A couple of studies have directly

compared the effect of 5-ALA vs. standard surgery under white light. The ALA study was a multi-centre Phase III study that randomised patients to either standard 'white light' resection or 'blue light' 5-ALA guided resection [16]. The rate of complete resection improved from 36% of cases using 'white light' to 65% of cases using 5-ALA. This improvement in extent of resection was reflected with a 19.9% improvement in progression free survival at 6 months for the 5-ALA group. There were no differences in the frequency of severe adverse events.

The VISIONA study was a multi-centre, retrospective observational cohort study that took data from 18 units in Spain and compared a cohort that had resection under 5-ALA and a cohort that did not [20]. They found 5-ALA improved the rate of complete resection from 45% in the 'white light' group to 67% in the 5-ALA group. This was associated with a 21% improvement in progression free survival at 6 months using 5-ALA. This study showed similar results could be obtained from standard care as reported in a clinical trial.

It must be stressed that 5-ALA is a tool, like other surgical adjuncts, that improves the extent of resection. Combining 5-ALA with other tools, for example intra-operative MRI, improves the rate of complete resection from 61.7% with 5-ALA alone up to 100% [21]. Similarly, it can increase the rate of complete resection using intra-operative MRI alone from 82% up to 100% with the addition of 5-ALA guidance [22]. Combining 5-ALA guided resections with intra-operative neurophysiology for brain mapping reported complete resection rates of 89% [18].

Safety of 5-ALA guided resections

The major concern of undertaking more extensive resections is the risk of damaging normal brain. It is now understood that resections of the fluorescent tumour extends beyond the contrast-enhanced tumour [23]. Studies suggest the rate of neurological deficit is low, but higher in patients with pre-existing deficits [18,20,20,24]. One study found that although 8.2% had deteriorated, 36% of patients had improved within a month of surgery [10].

The ALA study compared rates of complications between 'white light' surgery and 5-ALA fluorescence guided surgery [24]. They found similar adverse events (58.7% 5-ALA vs. 57.8% white light), neurological adverse events (42.8% vs. 44.5%), adverse events greater than Grade 3/4 (7% vs. 5.2%) and serious adverse events (29.9% in 5-ALA vs. 23.1% white light). The only difference in individual SAEs was for raised intracranial pressure in the white light group (2.3% in white light vs. 0% in 5-ALA group; p=0.04) - this reflects earlier tumour progression. Using the NIH-SS score, a measure of neurological deficits, showed more neurological deterioration in the 5-ALA patients at 48 hours post-op (26.2% vs. 14.5%; p=0.02). This difference was only seen in the cohort of patients with pre-existing neurological deficits that persisted after steroid therapy. This was no longer significant by one week. There was no difference in the Karnofsky performance status at 6 weeks and 3 months. At 6 months the 5-ALA arm tended to have less frequent deterioration in KPS – again this is related to the delayed progression in the 5-ALA group.

Surgery in eloquent areas is where you would expect more extensive resection would cause higher rates of neurological deterioration. Although there is a high rate of neurological deterioration by day 7 (64% of patients had deteriorated), this was temporary, and only 3% of patients had on going deficits by 90 days [25]. The group with permanent deficits were patients with pre-existing deficits or were undergoing surgery for recurrent disease. In this group of patients the rate of deficits does appear greater - Nabavi et al reported 39% of patients undergoing 5-ALA resection of recurrent tumours developed new deficits, suggesting fluorescent tumour infiltrating normal, functioning brain [13].

Cost effectiveness of 5-ALA fluorescence guided surgery

In current health care treatments need to be cost effective. A survey of UK neurosurgical units has shown that over a third do not use 5-ALA due to costs (unpublished data presented at the British Neuro-oncology Society Meeting, 2016, Leeds). Esteves et al published cost effectiveness data based on the ALA study, costed for the Portuguese Health Service [26]. They found the additional costs for the 5-ALA group of €1,487.97 - much of this is accounted for by additional chemotherapy cycles as the 5-ALA group remains progression-free for longer. They calculated the cost per quality adjusted life year (QALY) was €9,100 (range €8,282 - €21,314). These figures were remarkably similar to an analysis of the VISIONA study that reported an excess cost of €1,010 in the 5-ALA group and the cost per QALY of €9,021[27]. These figures are well below the £20,000 threshold that is commonly attributed to the National Institute of Health and Clinical Excellence.

Conclusion

There is now good evidence that 5-ALA can accurately detect tumour based on abnormalities of porphyrin metabolism. The use of 5-ALA guided resection improves the extent of resection of high grade gliomas and is safe, especially in patients who have no neurological deficit following steroid therapy. As extent of resection is the only prognostic factor of high grade gliomas that we can alter, and as it is cost-effective, 5-ALA should be the standard of care for all patients undergoing radical resection of high grade gliomas.

REFERENCES

1. Sanai N, Polley MY, McDermott MW, et al. *An extent of resection threshold for newly diagnosed glioblastomas.* Journal of Neurosurgery 2011; 115(1):3-8.
2. Brown TJ, Brennan MC, Li M, et al. *Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-analysis.* JAMA Oncol 2016.
3. Stummer W, Meinel T, Ewelt C, et al. *Prospective cohort study of radiotherapy with concomitant and adjuvant temozolomide chemotherapy for glioblastoma patients with no or minimal residual enhancing tumor load after surgery.* Journal of Neuro-Oncology 2012:1-9.
4. Albert FK, Forsting M, Sartor K, et al. *Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis.* Neurosurgery 1994; 34(1):45-60.
5. Stummer W, Stocker S, Wagner S, et al. *Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence.* Neurosurgery 1998; 42(3):518-25; discussion 525-6.
6. Stummer W, Stocker S, Novotny A, et al. *In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid.* Journal of photochemistry and photobiology B Biology 1998; 45(2-3):160-9.
7. Ennis SR, Novotny A, Xiang J, et al. *Transport of 5-aminolevulinic acid between blood and brain.* Brain Res 2003; 959(2):226-34.

8. Stummer W, Novotny A, Stepp H, et al. *Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients.* J Neurosurg 2000; 93(6):1003-1013.
9. Roberts DW, Valdes PA, Harris BT, et al. *Coregistered fluorescence-enhanced tumor resection of malignant glioma: relationships between delta-aminolevulinic acid-induced protoporphyrin IX fluorescence, magnetic resonance imaging enhancement, and neuropathological parameters.* Clinical article. J Neurosurg 2011; 114(3):595-603.
10. Diez Valle R, Tejada Solis S, Idoate Gastearena MA, et al. *Surgery guided by 5-aminolevulinic fluorescence in glioblastoma: volumetric analysis of extent of resection in single-center experience.* J Neurooncol 2011; 102(1):105-113.
11. Stummer W, Tonn JC, Goetz C, et al. *5-Aminolevulinic Acid-derived Tumor Fluorescence: The Diagnostic Accuracy of Visible Fluorescence Qualities as Corroborated by Spectrometry and Histology and Postoperative Imaging.* Neurosurgery 2014; 74(3):310-20.
12. Idoate MA, Diez Valle R, Echeveste J, et al. *Pathological characterization of the glioblastoma border as shown during surgery using 5-aminolevulinic acid-induced fluorescence.* Neuropathology : official journal of the Japanese Society of Neuropathology 2011; 31(6):575-82.
13. Nabavi A, Thurm H, Zountsas B, et al. *Five-aminolevulinic acid for fluorescence-guided resection of recurrent malignant gliomas: a phase ii study.* Neurosurgery 2009; 65(6):1070-1076; discussion 1076-1077.
14. Widhalm G, Wolfsberger S, Minchev G, et al. *5-Aminolevulinic acid is a promising marker for detection of anaplastic foci in diffusely infiltrating gliomas with nonsignificant contrast enhancement.* Cancer 2010; 116(6):1545-52.
15. Widhalm G, Minchev G, Woehrer A, et al. *Strong 5-aminolevulinic acid-induced fluorescence is a novel intraoperative marker for representative tissue samples in stereotactic brain tumor biopsies.* Neurosurg Rev 2012; 35(3):381-91; discussion 391.
16. Stummer W, Pichlmeier U, Meinel T, et al. *Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial.* Lancet Oncol 2006; 7(5):392-401.
17. Feigl GC, Ritz R, Moraes M, et al. *Resection of malignant brain tumors in eloquent cortical areas: a new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring.* J Neurosurg 2010; 113(2):352-7.
18. Schucht P, Beck J, Abu-Isa J, et al. *Gross total resection rates in contemporary glioblastoma surgery: results of an institutional protocol combining 5-aminolevulinic acid intraoperative fluorescence imaging and brain mapping.* Neurosurgery 2012; 71(5):927-35; discussion 935-36.
19. Tykocki T, Michalik R, Bonicki W, et al. *Fluorescence-guided resection of primary and recurrent malignant gliomas with 5-aminolevulinic acid. Preliminary results.* Neurologia i neurochirurgia polska 2012; 46(1):47-51.
20. Diez Valle R, Slof J, Galvan J, et al. *Observational, retrospective study of the effectiveness of 5-aminolevulinic acid in malignant glioma surgery in Spain (The VISIONA study).* Neurologia (Barcelona, Spain) 2014; 29(3):131-8.
21. Eyupoglu IY, Hore N, Savaskan NE, et al. *Improving the extent of malignant glioma resection by dual intraoperative visualization approach.* PloS one 2012; 7(9):e44885.
22. Coburger J, Engelke J, Scheuerle A, et al. *Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment.* Neurosurg Focus 2014; 36(2):E3.
23. Schucht P, Knittel S, Slotboom J, et al. *5-ALA complete resections go beyond MR contrast enhancement: shift corrected volumetric analysis of the extent of resection in surgery for glioblastoma.* Acta Neurochirurgica 2013.
24. Stummer W, Tonn JC, Mehdorn HM, et al. *Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study.* Clinical article. J Neurosurg 2011; 114(3):613-23.
25. Della Puppa A, De Pellegrin S, d'Avella E, et al. *5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature.* Acta Neurochir (Wien) 2013; 155(6):965-72; discussion 972.
26. Esteves S, Alves M, Castel-Branco M, et al. *A pilot cost-effectiveness analysis of treatments in newly diagnosed high-grade gliomas: the example of 5-aminolevulinic Acid compared with white-light surgery.* Neurosurgery 2015; 76(5):552-62.
27. Slof J, Diez Valle R, Galvan J. *Cost-effectiveness of 5-aminolevulinic acid-induced fluorescence in malignant glioma surgery.* Neurologia (Barcelona, Spain) 2015; 30(3):163-8.

Silver Jubilee celebrations for Clatterbridge Papillon Centre (1992-2017)

A team from Clatterbridge Cancer Centre led by Professor Arthur Sun Myint visited Lyon in France to study contact x-ray brachytherapy (CXB) also known as Papillon technique for rectal cancer. The Papillon facility was set up at Clatterbridge in 1992 and started treating patients with rectal cancer in 1993. Therapax (Gulmay, UK) machine was used initially until 2009. A new machine made by British company Arian was available from 2008 and the Papillon Plus prototype machine, first in the world, was used to start treating patients from October 2009. They have now treated over 1000 patients which is the world largest cohort of patients treated by contact x-ray brachytherapy. A new dedicated Papillon suite to treat rectal cancer patients was opened at Clatterbridge on 27th September by Sir Ian Gilmore (past President of the Royal College of Physicians). In 2014, Papillon suite received 'Macmillian-Quality Care Environment' award in recognition of their outstanding services in creating a quality environment for patients who travelled from all around the UK and other parts of the world. Clatterbridge trained clinicians, physicists and radiographers from other centres hoping to set up Papillon facilities in the UK and other countries since 2010. There are four centres in the UK with Papillon facilities and 12 around the world. NICE (National Institute for Health and Care Excellence) published their recommendation in September 2015 as IP 532. NICE recommend contact X-ray brachytherapy for patients with rectal cancer not suitable for surgery as a safe and effective treatment. The international contact radiotherapy network (ICONE) has set up an international randomised trial OPERA (Organ Preservation for Early Rectal Adenocarcinoma) which has started recruiting patients in France. We have now got ethical approval in the UK and hoping to start recruiting patients once the trial is in the NIHR portfolio, hopefully later this year.

The Papillon machine with Professor Sun Myint (lead Clinician in Papillon) and Kate Perkins (Papillon Specialist Radiographer).

The Papillon Centre at Clatterbridge

Papillon patients support group (PAPS) was set up in 2008 and Clatterbridge hold regular annual meetings which were well attended. Lead volunteer for PAPS Sue Davies was awarded a prestigious Macmillian volunteer of the year award in 2013. Lead Clinician Professor Sun Myint is a keen advocate for 'Patients' choice' and lobby all Government bodies and organisations in his travels around the world presenting a strong case on behalf of his patients. NHS England should consider expanding more facilities for rectal cancer patients using contact x-ray brachytherapy (Papillon) around the UK as the number of cases diagnosed with early rectal cancer suitable for Papillon is increasing through National Bowel Cancer Screening Programme (NBCSP) started since 2006. If there is residual cancer or local regrowth at a later date after Papillon, successful salvage surgery can be carried out without compromising the chancer of cure for patients wishing to avoid extirpative surgery and a stoma. The population is ageing and there are published evidence on surgical harm in older patients undergoing extirpative surgery. The quality of life following Papillon treatment can be much better and Macmillian Services is supporting a prospective survey as part of their 'Living beyond cancer' project. We hope that the new NICE colorectal guidelines (2018) will include Papillon as an option for treatment of patients with rectal cancer as this is still not regarded as a standard of care. NICE guidelines will change the standard of care in patients with rectal cancer not just in the UK but around the world.

Seeing is Believing ...

The Ariane Medical Systems Papillon+ system combines 30 years of clinical experience with 21st Century technology.

"Eye Guided" - High Dose, Low Energy Photons are delivered directly to the tumour or resected tumour bed ensuring high cancer cell kill with minimal healthy tissue damage.

One Platform – Many Solutions: The patented Papillon+ Micronode delivers curative treatments for Lower Rectal Tumours, Superficial Skin Cancers and Breast IORT in a matter of minutes.

Seeing Is Believing !

Papillon+™

Rectal Treatment

Breast Treatment

Skin Treatment

Ariane™
MEDICAL SYSTEMS

To see how these treatment solutions could benefit your MDT

Contact info@arianemedicalsystems.com
Visit www.arianemedicalsystems.com

Ariane Medical Systems Limited Tel: +44 (0) 1332 242258

A role for cholesterol in prostate cancer: a Boston-Ireland collaboration under the Professor John Fitzpatrick Fellowship

Emma H Allott,
Research Assistant Professor, Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Visiting Scientist, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, USA; and Irish Cancer Society John Fitzpatrick Research Fellow, School of Medicine, Trinity College Dublin, Ireland.

Lorelei A Mucci,
Associate Professor of Epidemiology, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, USA; Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School Boston, Boston, USA.

Christopher J Sweeney,
Associate Professor of Medicine, Harvard Medical School, Boston, USA; Medical Oncologist, Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Boston, USA.

Ray McDermott,
Consultant Medical Oncologist, The Adelaide and Meath Hospital, and The National Children's Hospital Tallaght, Dublin, Ireland.

Stephen Finn,
Associate Professor, School of Medicine, Trinity College Dublin, Dublin, Ireland; and Consultant Pathologist Department of Histopathology, Central Pathology Department, St James's Hospital, Ireland.

Financial support:
This work is supported by the Irish Cancer Society John Fitzpatrick Fellowship Programme under grant JFF16ALL, and the Dana-Farber Cancer Institute and Harvard T.H. Chan School of Public Health, and funded by Janssen-Cilag Ltd and Sanofi-Aventis Ireland Ltd.

Prostate cancer is a common and often chronic disease in Western society, and almost half of all male cancer survivors in both the United States (US) [1] and Ireland (http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_prostate_1.pdf) suffer from prostate cancer. Approximately one third of prostate cancer patients will experience recurrence within a decade of primary treatment. Androgen deprivation therapy (ADT) is one of the treatments for recurrent prostate cancer. When ADT is started after cancer can be seen on scans, resistance nearly always develops within 18 months, and 10-20% of patients will develop castrate resistant prostate cancer (CRPC) within five years of initial diagnosis – currently an incurable disease [2]. Response to therapy and time to disease progression varies between individuals and a number of lifestyle factors may contribute, including obesity and its associated co-morbidities.

According to the World Health Organization, approximately one third of US adults have a body mass index of ≥30 kg/m^2 and are therefore classified as obese, whereas one quarter of adults meet this definition in Ireland. Obesity is associated with more advanced prostate cancer at diagnosis, higher risk of recurrence and increased prostate cancer-specific mortality [3]. While the mechanisms contributing to the obesity-prostate cancer link are not completely understood, a number of obesity-associated co-morbidities can influence prostate tumorigenesis. These include dyslipidemia, a metabolic disorder characterised by elevated circulating levels of cholesterol and/or triglycerides (Table 1) that affects almost 40% of adults worldwide [4].

Dyslipidemia and prostate cancer: evidence from laboratory studies

Cholesterol is an essential plasma membrane component of animal cells, being crucial in maintaining cell membrane fluidity, and in regulating intracellular signalling processes. Relative to cells of other organs, normal prostate epithelial cells have high cholesterol content, which increases during progression to prostate cancer [5], suggesting that cholesterol accumulation may accelerate tumour progression. Metabolomic profiling of human prostate tumours indicated higher levels of cholesterol in prostate cancer bone metastases compared to benign or localized disease [6]. Epigenetic silencing of the cholesterol efflux transporter, ABCA1, resulted in

Table 1: Guidelines for serum lipids levels in men, according to the National Cholesterol Education Program [22], in milligrams per deciliter (units commonly used in US) and in millimoles per liter (units commonly used in Europe)

	Desirable	Borderline	Abnormal
Total cholesterol	<200 mg/dl <5.0 mmol/l	200-249 mg/dl 5.0-6.2 mmol/l	≥240 mg/dl ≥6.2 mmol/l
Low density lipoprotein	<130 mg/dl <3.3 mmol/l	130-159 mg/dl 3.3-4.1 mmol/l	≥160 mg/dl ≥4.1 mmol/l
High density lipoprotein	≥60 mg/dl ≥1.6 mmol/l	40-59 mg/dl 1.0-1.6 mmol/L	<40 mg/dl <1.0 mmol/L
Triglyceride	<150 mg/dl <1.7 mmol/l	150-199 mg/dl 1.7-2.3 mmol/l	≥200 mg/dl ≥2.3 mmol/l

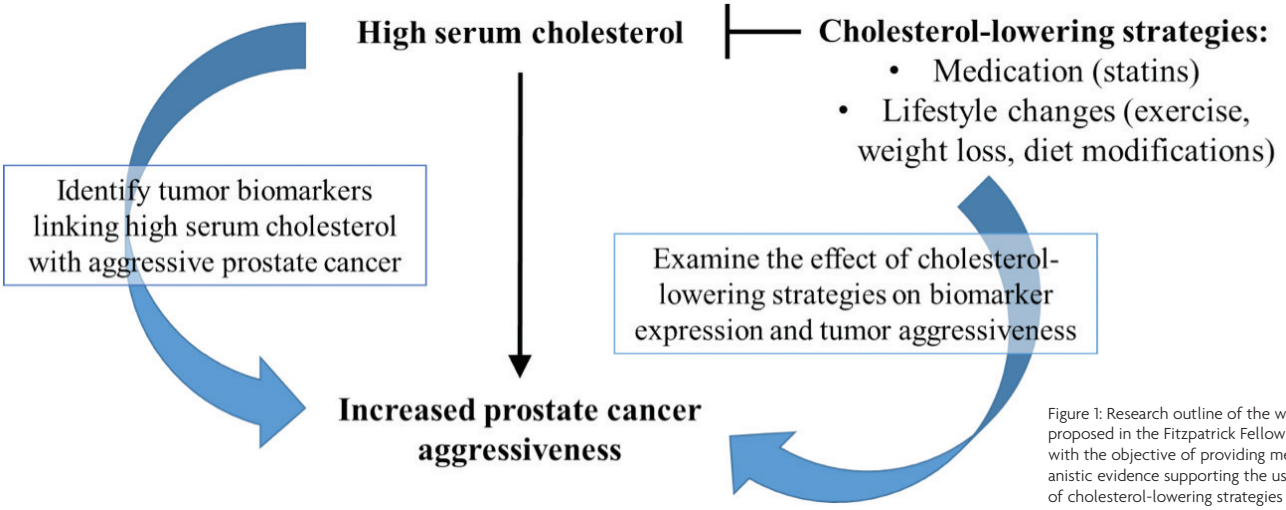


Figure 1: Research outline of the work proposed in the Fitzpatrick Fellowship, with the objective of providing mechanistic evidence supporting the use of cholesterol-lowering strategies to improve prostate cancer outcomes.

accumulation of intracellular cholesterol in prostate cancer cell lines, and was positively correlated with high Gleason grade in human prostate tumours [7]. Cholesterol is the precursor for androgen biosynthesis and may contribute to persistence of intratumoural androgens, despite achieving castrate serum levels with ADT. Indeed, high serum cholesterol increased intratumour androgen levels in mouse models of prostate cancer [8], and cholesterol-driven intratumoural de novo steroidogenesis was upregulated during progression from androgen-sensitive disease to CRPC in mice [9]. Lowering the level of serum cholesterol through dietary intervention and/or administration of the cholesterol uptake inhibitor, ezetimibe, reduced tumour androgen levels and slowed tumour growth rate in mouse prostate cancer [8]. In addition to its role as the precursor for androgen biosynthesis, cholesterol drives prostate cancer growth in mice by heightening inflammation and increasing Akt signalling [10], indicating several potential mechanisms contributing to a cholesterol-prostate cancer link.

Dyslipidemia and prostate cancer: evidence from epidemiologic studies

In support of laboratory evidence, epidemiology has shown that high serum cholesterol is associated with advanced prostate cancer, but not with all prostate cancer [11]. Although studies are few, epidemiologic data also suggest a positive association between elevated serum cholesterol and triglycerides and prostate cancer recurrence [12]. Several large prospective studies suggest a positive, albeit modest, association between dyslipidemia and prostate cancer-specific mortality. The UK-based Whitehall study, comprised of ~18,000 men and 600 prostate cancer deaths occurring during 40 years of follow-up, reported that high cholesterol was associated with a modestly elevated risk of prostate cancer-specific mortality [13]. In contrast, the Metabolic Syndrome and Cancer Project, comprising almost 300,000 Northern European men and over 1,000 prostate cancer deaths, reported similar rates of prostate cancer-specific mortality in men with normal or elevated triglyceride and cholesterol levels [14]. Finally, the findings of a large prospective study in the Asian-Pacific region indicated a positive association between high cholesterol and increased prostate cancer-specific mortality, but it was not statistically significant [15]. However, the strongest evidence for a cholesterol-prostate cancer link comes from studies of statins and prostate cancer. Statins are a class of medication that lower serum cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for cholesterol synthesis in the liver. They are among the most commonly-prescribed drugs in the US and Ireland, and are well-tolerated drugs, with few major side effects [16]. Of >30 observational studies on the use of statins and prostate cancer risk published to date, the majority support the hypothesis that statins reduce the risk of advanced prostate cancer. Other epidemiologic studies strongly support a role for statins in lowering prostate cancer-specific mortality [17]. These include an analysis of a population-based electronic database in the UK containing data from almost 12,000 men with prostate cancer, which found that taking statins reduced the risk of death from prostate cancer, with a larger effect in men who had commenced before prostate cancer diagnosis, compared with those who started taking statins after prostate cancer diagnosis [18]. Naturally there are the known benefits of controlling cholesterol levels for the purposes of cardiovascular disease prevention to consider.

A role for exercise and weight loss?

A number of lifestyle changes can help to lower cholesterol levels, including exercise and weight loss. Although obesity and increased co-morbidity effects relate to prostate cancer-specific mortality, the effect of weight loss on prostate cancer-specific outcomes has not been widely studied [11]. One goal of the Fitzpatrick Fellowship is to identify tumour biomarkers associated with dyslipidemia where their expression is counteracted by cholesterol-lowering lifestyle changes, including statins, exercise and/or weight loss (Figure 1). This objective should be achieved in an observational setting using the Harvard-based Health Professionals Follow-up Study (HPFS), where biennial questionnaires are used to record changes in anthropometric characteristics and physical activity levels with time, and to assess baseline obesity status and

calculate weight change in the years preceding diagnosis of prostate cancer. This will also be studied in a clinical trial setting using ExPeCT, an ongoing exercise intervention trial in Irish patients with metastatic prostate cancer.

Public health relevance

Understanding the effects of dyslipidemia in prostate cancer will be important for improving public health. The most recent estimate of the global prevalence of high cholesterol was 39%, with the highest prevalence in Europe (54% for both sexes), followed by the US (48% for both sexes; WHO - http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/). The prevalence of dyslipidemia is even higher among men with advanced prostate cancer and CRPC, given that long-term ADT exacerbates metabolic abnormalities [19]. As such, understanding mechanisms linking dyslipidemia with prostate cancer progression will be of considerable importance for a large proportion of prostate cancer patients. Furthermore, high cholesterol can be effectively treated in the vast majority of individuals by dietary changes (e.g. lowering saturated fat intake), exercise and weight loss, and/or cholesterol-lowering medication (statins). Therefore, in contrast to established risk factors for prostate cancer (age, African American race, and family history of prostate cancer; none of which can be modified), patients can try to normalize their lipid levels. Prostate cancer diagnosis can be a "teachable moment" (i.e. an event which could trigger a change in patient behaviour); if a causal link could be established between dyslipidemia and progression, this might influence treatment protocols. Finally, it is estimated that 45% of deaths worldwide can be attributed to either cardiovascular disease or cancer [20], with prostate cancer being the second most common cause of male cancer deaths [21]. Therefore, understanding the role of dyslipidemia as a shared risk factor for both of these common causes of mortality has potential not only to extend prostate cancer-specific survival, but to improve quality of life and extend overall survival in these patients.

Conclusions

Identification of risk factors contributing to therapeutic resistance and disease progression is an important challenge in prostate cancer research. Treatment strategies for CRPC are evolving, with some novel agents showing improvements in overall survival rates. However, it is currently impossible to predict individual response to therapy and there is no way of selecting which patients should receive specific therapies. The contribution of the work outlined in the Fitzpatrick Fellowship is expected to be the identification of dyslipidemia-associated tumour biomarkers that can be predictive of response to therapy and prostate cancer-specific outcomes, and that can be reversible through statins, exercise and/or weight loss. This contribution will be important in customising therapies to individuals likely to show the best responses, alongside complementary approaches that will prolong survival of prostate cancer patients. The work proposed in this Fitzpatrick Fellowship bridges epidemiology and molecular biology, linking colleagues in biostatistics, molecular pathology, cancer biology and genetics in Boston and Ireland. A notable strength of the Harvard School of Public Health is its integration into the Dana Farber/Harvard Cancer Centre, the largest comprehensive cancer centre in the world, increasing opportunities for collaboration with clinical colleagues, and acting as a venue for epidemiologic studies, including the HPFS. Finally, the Fitzpatrick Fellowship will strengthen existing ties between the Harvard School of Public Health and the Institute for Molecular Medicine at Trinity College Dublin in cancer biology, epidemiology, clinical practice and population health, with the ultimate goal of making a real and lasting difference to prostate cancer patients and their families on both sides of the Atlantic and worldwide.

REFERENCES

1. American Cancer Society. *Cancer Treatment and Survivorship Facts & Figures 2016-2017.* Atlanta: American Cancer Society 2016.
2. Kirby M, Hirst C, and Crawford ED. *Characterising the castration-resistant prostate cancer population: a systematic review.* Int J Clin Pract 2011;65(11):1180-92.
3. Allott EH, Masko EM, and Freedland SJ. *Obesity and prostate cancer: weighing the evidence.* Eur Urol, 2013;63(5):800-9.
4. Fryar CD, Chen TC, and Li X. *Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010.* NCHS Data Brief 2012;(103):1-8.
5. Krycer JR and Brown AJ. *Cholesterol accumulation in prostate cancer: a classic observation from a modern perspective.* Biochim Biophys Acta 2013;1835(2):219-29.
6. Thysell E, et al. *Metabolomic characterization of human prostate cancer bone metastases reveals increased levels of cholesterol.* PLoS One 2010;5(12):e14175.
7. Solomon KR, et al. *Words of wisdom. Re: Dysregulation of cholesterol homeostasis in human prostate cancer through loss of ABCA1.* Eur Urol 2013;63(6):1128-9.
8. Mostaghel EA, et al. *Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors.* PLoS One 2012;7(1):e30062.
9. Locke JA, et al. *Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer.* Cancer Res 2008;68(15):6407-15.
10. Zhuang L, et al. *Cholesterol-rich lipid rafts mediate akt-regulated survival in prostate cancer cells.* Cancer Res 2002;62(8):2227-31.
11. Allott EH and Hursting SD. *Obesity and cancer: mechanistic insights from transdisciplinary studies.* Endocr Relat Cancer 2015;22(6):R365-86.
12. Allott EH, et al. *Serum Lipid Profile and Risk of Prostate Cancer Recurrence: Results from the SEARCH Database.* Cancer Epidemiol Biomarkers Prev 2014;23(11):2349-56.
13. Batty GD, et al. *Modifiable risk factors for prostate cancer mortality in London: forty years of follow-up in the Whitehall study.* Cancer Causes Control 2011;22(2):311-8.
14. Haggstrom C, et al. *Prostate cancer, prostate cancer death, and death from other causes, among men with metabolic aberrations.* Epidemiology 2014;25(6):823-8.
15. Huxley R. *The impact of modifiable risk factors on mortality from prostate cancer in populations of the Asia-Pacific region.* Asian Pac J Cancer Prev 2007;8(2):199-205.
16. Gu Q, Paulose-Ram R, Burt VL, et al. *Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012.* NCHS data brief, no 177. Hyattsville, MD: National Center for Health Statistics 2014.
17. Alfaqih MA, et al. *The current evidence on statin use and prostate cancer prevention: are we there yet?* Nat Rev Urol, 2016.
18. Yu O, et al. *Use of statins and the risk of death in patients with prostate cancer.* J Clin Oncol 2014;32(1):5-11.
19. Levine GN, et al. *Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology.* CA Cancer J Clin 2010; 60(3):194-201.
20. Heron M. Deaths: *Leading Causes for 2011.* Natl Vital Stat Rep 2015;64(7):1-96.
21. Siegel RL, Miller KD, and Jemal A. *Cancer statistics 2015.* CA Cancer J Clin 2015;65(1):5-29.
22. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.* Circulation 2002;106(25):3143-421.

Dr Declan McKenna
Lecturer,
Genomic Medicine Research Group, School of Biomedical Sciences, Ulster University, Coleraine, UK.

Correspondence address:
E: dj.mckenna@ulster.ac.uk

Improving Hormone Therapy For Prostate Cancer

Prostate cancer is one of the most common cancers in men, with 1 in 8 men in the UK estimated to develop the disease at some point in their lives. However, thanks to better detection methods and treatment options, 10-year survival rates have tripled to almost 85% over the past 40 years, illustrating that prostate cancer can often be successfully treated [1]. Nevertheless, there remain some significant challenges to overcome. Diagnosis still relies heavily on detection of serum Prostate Specific Antigen (PSA) levels, but this test is neither sensitive nor specific enough, leading to false negatives and false positives. Moreover, PSA testing still cannot accurately differentiate between a tumour which is benign and one which is potentially metastatic, meaning some men get unnecessarily treated [2]. Grading and staging through biopsy examination will help determine the course of treatment, which may include surgery, radiotherapy, hormonal therapy and chemotherapy, or a strategic combination of the above. However, prostate cancer is widely variable to therapy, in that two apparently similar cases may respond very differently to the same regimen. So although the disease is now more manageable than ever before, work is needed to improve methods of detection and customising treatment for each prostate cancer patient. In this short review, the challenges and opportunities for improving the hormone therapy in prostate cancer treatment are discussed.

Hormone Therapy for Prostate Cancer

When Dr Charles Huggins took up a new post at the University of Chicago in 1927, he had little interest in cancer biology, making him a most unlikely candidate to revolutionise prostate cancer therapy. However, when he discovered that prostate cells are dependent on testosterone for growth, he wondered if depriving prostate tumours of the hormone could be a way to treat the cancer. He subsequently demonstrated that surgical castration of dogs with prostate cancer could indeed slow tumour growth, an effect subsequently shown to work in human patients. He then progressed to show that injection of female hormones (estrogens) could cancel out the effect of testosterone [3]. 'Chemical castration', as he called it, could be used to effectively suppress tumour growth in patients with prostate cancer, with minimal side-effects. It was a ground-breaking discovery that won him the Nobel Prize in 1966 and formed the basis for androgen deprivation therapy (ADT) [4].

Nowadays, several clinically available drugs are available for use in ADT and others are in development. For localised, early-stage prostate cancer, ADT generally involves suppressing testosterone production by interfering with the mechanisms which regulate its biosynthesis in the body. Luteinizing hormone-releasing hormone (LHRH) agonists or gonadotropin-releasing hormone (GnRH) inhibitors stop the pituitary gland producing luteinizing hormone (LH) needed to stimulate testosterone production in the testes. LNRH agonists are often given in combination with an anti-androgen, a drug which competitively blocks testosterone from binding to the androgen receptor (AR), thereby inhibiting AR-dependent growth signalling. For locally advanced prostate cancer anti-androgens are generally the favoured option. Notably, ADT for localised and locally advanced prostate cancer can be used in combination with radiotherapy, as several clinical trials over the past 30 years have shown that this approach can delay tumour progression compared to radiotherapy alone [5].

However, although patients receiving ADT for early-stage disease initially respond to treatment, they typically relapse within 2 years to castrate-resistant prostate cancer (CRPC), as mechanisms of androgen independence emerge in the tumour cell population. Historically, this would have meant moving to chemotherapy, but two ADT agents have recently shown benefit in management of later-stage metastatic CRPC (mCRPC). Enzalutamide is a second-generation anti-androgen, whereas abiraterone inhibits CYP171A, a key enzyme in the synthesis of testosterone. Results to date are encouraging and ongoing trials continue to track how these drugs can benefit patients with mCPRC [6] (Table 1). Thus, ADT continues to be the mainstay therapy for the management of prostate cancer at its various stages, and targeting AR axis signalling remains the focus for development of new ADT drugs [7].

Overcoming resistance to ADT

Nonetheless, the problem of developing ADT resistance and progression to mCPRC

Table 1. Prostate Cancer Trials open to recruitment in Northern Ireland (From NI Cancer Trials Centre December 2016)	
Trial Name	**Aim of Trial**
Stampede	Systemic Therapy in Advancing or Metastatic Prostate cancer - Evaluation of Drug Efficacy
UKGPCS	UK Genetics Prostate Cancer Study
Radicals	Radiotherapy and Androgen Deprivation in Combination after Local Surgery. A Randomised Controlled Trial in Prostate Cancer
Rapper	Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy
PROMPTS	prospective randomised phase III study of observation versus screening MRI and pre-emptive treatment in castrate resistant prostate cancer patients with spinal metastasis
PROSPER	a multi-national, Phase III, randomised, double-blind, placebo-controlled, efficacy and safety study of Enzalutamide in patients with non-metastatic castration-resistant prostate cancer
TOPARP	a phase II trial of Olaparib in patients with advanced castration resistant prostate cancer
PACE	international randomised study of laparoscopic prostatectomy vs stereotactic body radiotherapy (SBRT) and conventionally fractionated radiotherapy vs SBRT for early stage organ-confined prostate cancer
CASPIR	calcifications as an alternative to surgically implanted fiducial markers for prostate image guided radiotherapy (CASPIR) : a prospective feasiblity study
ADRRAD	neo-adjuvant Androgen Deprivation therapy, pelivic Radiotherapy and RADium-223 for new presentation T1-4 NO/1 M1B adenocarcinoma of prostate
LAPCD	Life After Prostate Cancer Diagnosis
SPORT High-Risk Trial	a randomised feasibility study evaluating Stereotactic Prostate Radio Therapy in high-risk localised prostate cancer with or without elective nodal irradiation

remains a major clinical obstacle to successful treatment of prostate cancer. Numerous cellular alterations including gene mutation, AR amplification, bypass pathways, ligand-independent activation and growth of cancer stem cells can all produce tumour cells that are no longer dependent on testosterone for growth and are more likely to develop into incurable disease. The driving forces underlying these changes remain elusive and the focus of much research.

In our laboratory at Ulster University (UU), research funded by Prostate Cancer UK is focused on how tumour hypoxia may exert a selective pressure that encourages the growth of cancer cells with increased metastatic potential. Low oxygen levels are a common feature of solid tumours and have been repeatedly linked to tumour progression in several cancers [8]. Using xenograft mouse models of prostate cancer, we found that an anti-androgen drug, bicalutamide, actually induces a profound hypoxia by collapsing the tumour vasculature, resulting in an upregulation of pro-survival genes by hypoxia-resistant cells within the tumour and increased metastatic potential [9,10]. This may help explain why patients relapse after initially successful response, making it necessary to consider treatment strategies that can target the resistant cells escaping hormone therapy.

One way of doing this is to investigate the combination of ADT with new drugs. At UU, we have recently reported that a novel hypoxia-activated prodrug (HAP) improves the ability of bicalutamide to control growth of human prostate tumours in mice [10]. This data suggests that the HAP becomes activated to its cytotoxic form in the hypoxic conditions induced by bicalutamide treatment, and kills resistant cells that would otherwise survive the hormone treatment. This study corroborates similar experimental findings from other pre-clinical studies that emphasise that physiological and molecular changes taking place in individual tumours in response to treatment should receive careful consideration in developing therapeutic regimens. Our on-going and planned work now intends to demonstrate the potential of this new drug in combination with other ADT drugs, such as enzalutamide.

This is timely work as the idea of combinatorial drug treatment has gained considerable momentum in recent years. In particular, recent results from the CHAARTED [11] and STAMPEDE [12] clinical trials have shown that use of docetaxel in combination with ADT improved relapse-free survival in patients with high-risk localised prostate cancer, proving that combining ADT with other types of drug can benefit prostate cancer sufferers. Similar on-going trials are investigating both the combination and the scheduling of different chemotherapeutic drugs (and/or radiation) with ADT on patient relapse and overall survival (Table 1). However, improved ways of predicting which patients will respond to which drugs is needed. Making the right decisions on what drug to use, when to treat, who to treat and, importantly, who not to treat, require better knowledge about the mechanisms that drive prostate cancer progression in order to improve patient stratification in the clinic.

Personalised Medicine

The drive towards personalised medicine depends on the discovery of biomarkers that can allow molecular stratification of patients. Such information is likely to reside in the vast arrays of data detailing the specific genetic characteristics of individual prostate tumours gathered from genomic profiling in recent years. Comprehensive bioinformatics analyses of the data shows that a wide molecular diversity exists in human prostate tumours [13]. Such tumour heterogeneity may help explain why patients presenting with pathologically similar tumours can respond very differently to the same course of treatment. For example, primary prostate cancers are highly variable in AR activity, with increased AR-dependent signalling linked to gene mutations in SPOP and FOXA1 [13]. Knowing whether a tumour carries these mutations or not can help determine the most appropriate ADT approach for a patient and subsequent tracking of those gene mutations can

inform adaptive drug administration. Likewise, knowing the mutational status of the AR gene itself will be critical in predicting treatment outcome [7,13]. For instance, enzalutamide cannot bind to an abnormal splice variant of the AR called AR-V7; patients harbouring this mutation would be unlikely to respond to that particular drug, emphasising the need to stratify patients by molecular profiles. Indeed, AR-V7 can be detected in patient blood samples and efforts to validate this screening for clinical application are underway [14].

Non-invasive biomarkers that can be measured in biofluids are an attractive option for clinical use. We are encouraged by the potential of microRNAs as markers of prostate progression and treatment response. These small RNA molecules are important regulators of cell function and many of them are aberrantly expressed in prostate cancer. Significantly, they are much more stably preserved than other RNA species in clinical samples, including fresh and fixed tissues, serum and urine, and can be readily detected using highly specific and sensitive PCR-based assays. Thus, both retrospective and prospective studies can determine the value of these as biomarkers of prostate cancer in different patient samples. Early evidence suggests that they can be used as circulating serum markers that predict treatment outcome [15]; our research effort is focused on identifying other microRNAs that have similar potential as serum-based biomarkers [16].

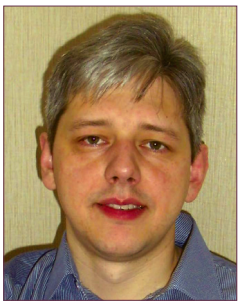
Conclusions

Improving ADT by developing precision medicine for individual patients is no small undertaking, but it is not an unrealistic proposition. Across the world, clinicians, researchers and industry are developing innovative ways to improve management of prostate cancer, and prostate cancer patients have more informed opportunities to participate in clinical trials. Treatment of prostate cancer continues to make huge strides since Charles Huggins' breakthrough work, but his words of wisdom remain as relevant as ever. "Discovery is our business," he once told his colleagues. "Make damn good discoveries." As a research community, we are aiming to make discoveries so good that few men need die from prostate cancer in future.

REFERENCES

1. Cancer Research UK Prostate Cancer Statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer [Accessed 23 January 2017]
2. Albin RJ and Piana R. *The Great Prostate Hoax: How Big Medicine Hijacked the PSA Test and Caused a Public Health Disaster.* 2014; New York, NY: St Martin's Press.
3. Huggins C, Stevens RE, Hodges CV. *Studies on prostatic cancerii. The effects of castration on advanced carcinoma of the prostate gland.* Arch Surg 1941; 43(2):209-223.
4. Hansson N, Moll F, Schultheiss D, et al. *Remembering Charles B. Huggins' Nobel Prize for Hormonal Treatment of Prostatic Cancer at its 50th Anniversary.* Eur Urol 2016; 69(6):971-2.
5. D'Angelillo RM, Franco P, De Bari B, et al. *Combination of androgen deprivation therapy and radiotherapy for localized prostate cancer in the contemporary era.* Crit Rev Oncol Hematol 2015; 93(2):136-48.
6. Northern Ireland Cancer Trials Centre (2017). *Prostate Cancer Trials open to recruitment.* Available at: http://www.qub.ac.uk/research-centres/nictc/ClinicalTrials/Bycancertype/ProstateCancer/ [Accessed 19 January 2017]
7. Jentzmik F, Azoitei A, Zengerling F, et al. *Androgen receptor aberrations in the era of abiraterone and enzalutamide.* World J Urol 2015; 34(3):297-303.
8. Muz B, de la Puente P, Azab F, et al. *The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy.* Hypoxia 2015; 3:83-92.
9. Byrne NM, Nesbitt H, Ming L, et al. *Androgen deprivation in LNCaP prostate tumor xenografts induces vascular changes and hypoxic stress resulting in promotion of epithelial to mesenchymal transition.* Br J Cancer 2016; 114:659-68.
10. Nesbitt H, Byrne NM, Williams N, et al. *Targeting hypoxic prostate tumours using the novel hypoxia-activated prodrug OCT1002 inhibits expression of genes associated with malignant progression.* Clin Cancer Res 2016; Oct 3. Epub ahead of print. DOI: 10.1158/1078-0432.CCR-16-1361
11. Sweeney CJ, Chen YH, Carducci M, et al. *Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer.* N Engl J Med 2015; 373(8):737-46.
12. James ND, Sydes MR, Clarke NW, et al. *Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial.* Lancet 2016; 387:1163-77.
13. Cancer Genome Atlas Research Network. *The Molecular Taxonomy of Primary Prostate Cancer.* Cell 2015; 163(4):1011-25.
14. Ciccarese C, Santoni M, Brunelli M, et al. *AR-V7 and prostate cancer: The watershed for treatment selection?* Cancer Treat Rev 2016;43:27-35.
15. Matin F, Jeet V, Clements JA, et al. *MicroRNA Theranostics in Prostate Cancer Precision Medicine.* Clin Chem 2016; 62(10):1318-33.
16. Lynch SM, O'Neill KM, McKenna MM, et al. *Regulation of miR-200c and miR-141 by methylation in prostate cancer.* Prostate 2016;76(13):1146-59.

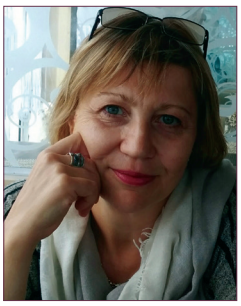
Possibilities of Predicting Post-operative Peritoneal Dissemination in Gastric Adenocarcinoma



Reutovich M Yu PhD Med,
Associate Professor,
NN Alexandrov National Cancer Centre, Minsk region, Republic of Belarus

Correspondence address
E: mihail_revtovich@yahoo.com

Shmak AI DSc (Med.),
NN Alexandrov National Cancer Centre, Minsk region, Republic of Belarus



Krasko OV PhD (Techn),
Associate Professor,
United Institute of Informatics Problems of the National Academy of Sciences of Belarus, Minsk, Republic of Belarus.

The peritoneum is the most frequent site of recurrence in radically operated gastric cancer patients [1]. It is caused either by residual micrometastases or by free-floating carcinoma cells already existing in the peritoneal cavity or by both. With regard to predictors for peritoneal carcinomatosis, no valid prognostic markers are currently available [2]. There are several quantitative prognostic indicators that serve as guidelines for selecting a treatment to maximise the benefits of therapy, but not for predicting dissemination [3]. Hence, identification of suitable biomarkers for early prediction of peritoneal recurrence and for prognosis is important in the overall management of patients with advanced gastric cancer.

Some researchers think that the appearance of free-floating carcinoma cells in the abdominal cavity is a starting-point in the formation of carcinomatosis in gastric cancer [4]. Cytological examination of peritoneal washings is the gold standard for diagnosing free tumor cells in the abdominal cavity; however, peritoneal wash cytology has a relatively low sensitivity ranging, from 10 to 33% in detecting these cells in patients with serosal invasion [5]. The sensitivity is much lower (5-15%) when macroscopic signs of dissemination are absent after curative resection [6].

The majority of cases with positive cytology of peritoneal washings (PW) develop peritoneal metastasis. According to Li et al. [7], the 1-, 3-, and 5-year survival rates are 53.3, 13.3, and 0%, respectively, in patients with positive peritoneal cytology, thus being significantly lower than 87.8, 71.4 and 55.1 in those with negative cytological findings ($p_{log\text{-}rank}<0.5$), although peritoneal recurrence also occurs in patients with negative cytological results. These results confirm that cytological examination lacks sensitivity for detecting residual cancer cells and predicting peritoneal spread [8]. Other recent studies on molecular diagnosis using the reverse transcriptase-polymerase chain reaction (RT-PCR) have been employed for the detection of free cancer cells, due to its high sensitivity [9-18]. The results of RT-PCR of PW correlate strongly with peritoneal recurrence and prognosis after curative surgery in patients of advanced gastric cancer [9-11]. A large number of molecular markers have been described in literature, the detection of which with RT-PCR in PW has to some extent been related to the progression of gastric cancer. Among them, *carcinoembryonic antigen (CEA)* is currently the standard molecular marker for the detection of gastric cancer micrometastases; however, it is not always expressed in gastric adenocarcinoma, but is weakly expressed in mesothelial cells, making it difficult to avoid false-positive and false-negative results using *CEA* as single marker.

When choosing a genetic marker for peritoneal dissemination, genes should be expressed in cancer cells higher than in mesothelial cells [12]. To improve the accuracy of prognostication, a possibility of expression of the *MMP-7* gene in a PW has been investigated [10]. *MMP-7* (*matrilysin*) gene is expressed mainly by tumour cells and is not secreted by the normal gastric mucosa [14]. The sensitivity of predicting peritoneal dissemination by cytology and *MMP-7* RT-PCR assay are 46 and 33%, respectively, but combined analysis using both parameters has improved the sensitivity to 62%. Better results for sensitivity and specificity as compared to *CEA mRNA* were obtained by Miyagawa et al. [12] in evaluating the expression of the *Regenerating gene type IV (RegIV)*. Sensitivity and specificity for RegIV are both 93%, whereas they are 73 and 91%, respectively, for *CEA mRNA*, with a combination of both markers increasing accuracy of diagnosis of micrometastases to 100%. Jeon et al. [11] used *CEA* and *melanoma-associated gene (MAGE)* RT-PCR for detecting peritoneal metastasis of gastric carcinoma. The sensitivity and specificity of the *CEA* RT-PCR assay for recurrence in this study were 70.6% (12/17) and 74.0% (74/100), respectively, and the sensitivity and specificity of *MAGE* expression for recurrence were 58.8% (10/17) and 99% (99/100), respectively. There was an improvement in specificity of *MAGE* expression compared to *CEA*; despite this, the sensitivity of *MAGE* was rather low.

It is clear from the above that the use of tumor-specific markers does not significantly improve the sensitivity and specificity compared to *CEA*. A possible explanation is that the expression level of a single gene is heterogeneous, and the limited sensitivity obviates its use alone. To improve the sensitivity and specificity of the mRNA detection approach, multiplex PCR may be more clinically useful in capturing intraperitoneal free cancer cell [16]. Dalal [13] reported that when RT-PCR for *CK20 mRNA* of 63% sensitivity and 91% specificity were combined with *CEA mRNA*, multivariate analysis identified the presence of both markers as a significant independent prognostic determinant [13]. A combination of *CEA mRNA*, *cytokeratin mRNA20*, *survivin* and *MUC2*, as well as a combination of any 3 of them helped diagnose free tumor cells in the abdominal cavity at 100% sensitivity and 71% specificity. Okada et al. [9] provided data on the comparative evaluation of survival for different number of expressed genes

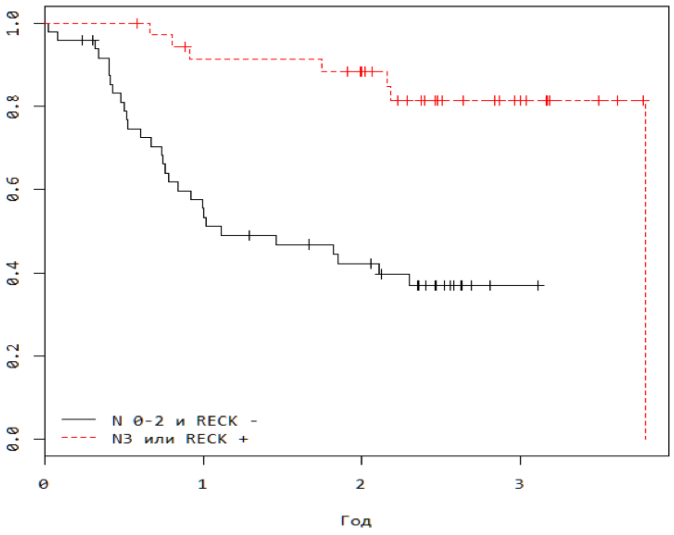


Figure 1: Dissemination free survival in patients with different methylation status of the *RECK* gene in PLF, and with varying degrees of metastatic involvement of the regional lymph node (pN)

- with 2 markers expressed out of the 3 (*CEA mRNA, CK20 mRNA, IMP-3*); survival was statistically considerably lower than when using only one gene ($p_{log\text{-}rank}<0.5$). Mori K et al. [15] support and second this after using a combination of *CK20*, *FABP1*, *MUC2*, *TFF1* and *TFF2*, which increase sensitivity and specificity in diagnosing free tumor cells in peritoneal flushes. When a combination of 5 genes was used, the sensitivity reached 83%, while the specificity reached 91-100%, whereas when using *CEA mRNA*, the sensitivity and specificity amounted to 94 and 83%, respectively. These studies resulted in creation of a biochip (microarray chip containing 10 marker genes as a "MiniChip"), which increases sensitivity and specificity in contrast to the traditional cytological studies aimed at spotting free tumor cells in the abdominal cavity [18].

At the NN Alexandrov National Cancer Center of Belarus, we have assessed the prognostic significance of the status of methylation of the *RECK gene* (*reversion-inducing cysteine-rich protein with Kazal motifs*) in peritoneal lavage fluid (PLF) taken after lymph node dissection in 85 patients radically operated on for gastric cancer. Statistically significant growth risk exists that the disease will progress with peritoneal dissemination in the case of a positive methylation status of the *RECK* gene accompanied by the presence of a massive metastatic lesion of the regional lymph node (pN3). Based on an estimation of the probability of peritoneal dissemination development by Kaplan-Meyer, if there is no methylation of the *RECK* promoter site in washes after lymph node dissection (*RECK*– washes), while metastatic lymph node corresponds to pN0-2, the probability of developing peritoneal dissemination is 14% within 1 year, 17% within 2 years, 21% within 3 years, which corresponds to the standard risk of peritoneal dissemination development. With the increase in the degree of metastatic lesion of the regional lymphocyte to pN3 (i.e. in a case of available metastases in 7 or more regional lymph nodes) and/ or in a case of *RECK* + washings after dissection, the probability of peritoneal dissemination by Kaplan-Meyer is 48% in patients within 1 year, 55% within 2 years, 59% of patients within 3 years, which shows a high risk of its development. The sensitivity of the proposed prognostic method is 78.8%, specificity is 59.6%, diagnostic accuracy is 67.1%, informativeness (the area under the ROC curve) is 0.73; 95% confidence interval (0.62-0.83).

Clinical application of the method described above makes it possible just at the stage of surgical operation for stomach cancer to pinpoint groups of patients having high risk of peritoneal dissemination post-operatively, with a view of performing an in-depth examination part of dynamic monitoring, and also for the purpose of timely therapeutic treatment aimed at preventing acceleration of this particular disease (adjuvant intraperitoneal chemotherapy).

Thus, analysis of published data proves that a painstaking search is in progress for ways of predicting one of the most common variants of gastric cancer acceleration – peritoneal dissemination. Despite extensive research, this problem is far from being solved and requires further investigation. Detection of a high risk of developing peritoneal dissemination following radical surgical treatment of gastric cancer will permit the use of a case-by-case approach to planning adjuvant treatment with a view of preventing development of this kind of progression.

REFERENCES

1. Yoo CH, Noh SH, Shin DW et al. *Recurrence following curative resection for gastric carcinoma.* Brit J Surg 2000; 87: 236–42.
2. Zieker D, Königsrainer I, Traub F et al. *PGK1 a Potential Marker for Peritoneal Dissemination in Gastric Cancer.* Cell Physiol Biochem 2008; 21: 429–36.
3. Harmon RL, Sugarbaker PH. *Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer.* Int Semin Surg Oncol: ISSO. 2005;2:3. doi:10.1186/1477-7800-2-3.
4. *Japanese Gastric Cancer Association Japanese classification of gastric carcinoma.* 2nd English ed. Gastric Cancer 2011; 14: 101–112.
5. Kodera Y, Yamamura Y, Shimizu Y, et al. *Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection.* J Surg Oncol 1999; 72: 60–6.
6. Bentrem D, Wilton A, Mazumdar M, et al. *The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection.* Ann Surg Oncol 2005; 12: 347–53.
7. Li JK, Zheng M, Miao CW et al. *Peritoneal lavage cytology and carcinoembryonic antigen determination in predicting peritoneal metastasis and prognosis of gastric cancer.* World J Gastroenterol 2005; 11(46): 7374–7.
8. Bando E, Yonemura I, Takeshita I et al. *Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma.* Am J Surg 1999; 178(3): 256–62.
9. Okada K, Fujiwara Y, Nakamura Y et al. *Oncofetal protein, IMP-3, a potential marker for prediction of postoperative peritoneal dissemination in gastric adenocarcinoma.* J Surg Oncol 2012; 105(8) 780–5.
10. Yonemura Y, Fujimura T, Ninomiya I et al. *Prediction of peritoneal micrometastasis by peritoneal lavaged cytology and reverse transcriptase-polymerase chain reaction for matrix metalloproteinase-7 mRNA.* Clin Cancer Res 2001; 7(6): 1647–53.
11. Jeon C-H, Kim I-H, Chae H-D. *Prognostic Value of Genetic Detection Using CEA and MAGE in Peritoneal Washes With Gastric Carcinoma After Curative Resection. Result of a 3-Year Follow-Up.* Medicine 2014; 93(11): e83. DOI: 10.1097/MD.0000000000000083.
12. Miyagawa K, Sakakura C, Nakashima S et al. *Overexpression of RegIV in Peritoneal Dissemination of Gastric Cancer and Its Potential as A Novel Marker for the Detection of Peritoneal Micrometastasis.* Anticancer Res 2008; 28: 1169–80.
13. Dalal KM, Woo Y, Kelly K et al. *Detection of micrometastases in peritoneal washings of gastric cancer patients by the reverse transcriptase polymerase chain reaction.* Gastric Cancer 2008; 11(4): 206–213. doi:10.1007/s10120-008-0483-6.
14. Kuang R-G, Wu H-X, Hao G-X et al. *Expression and significance of IGF-2, PCNA, MMP-7, and αactin in gastric carcinoma with Lauren classification.*/ Turk J Gastroenterol 2014; 24(2): 99–108.
15. Mori K, Suzuki T, Uozaki H et al. *Detection of minimal gastric cancer cells in peritoneal washings by focused microarray analysis with multiple markers: clinical implications.* Ann Surg Oncol 2007; 14: 1694–702.
16. Kagawa S, Shigeyasu K, Ishida M et al. *Molecular diagnosis and therapy for occult peritoneal metastasis in gastric cancer patients.* World J Gastroenterol 2014; 20(47): 17796–803.
17. Mori K, Aoyagi K, Ueda T et al. *Highly specific marker genes for detecting minimal gastric cancer cells in cytology negative peritoneal washings.* Biochem Biophys Res Commun 2004; 313: 931–7.

Robotic Surgery for Head and Neck Cancer

George Garas, MRCS (Eng)
Hon. Clinical Lecturer, Surgery and Cancer, Imperial College London, UK.

Correspondence
E: g.garas@imperial.ac.uk

Neil Tolley, FRCS (Eng and Ed)
Professor, Surgery and Cancer, Imperial College London, UK.

Background

Following the introduction of the da Vinci® surgical robot (Intuitive Surgical®, Inc., Sunnyvale, CA, US) in 1997, the FDA gave its approval in 2000 [1]. It has since been used in a variety of surgical specialties, including general surgery, urology, cardiothoracic surgery and gynecology, facilitating conventional laparoscopic and thoracoscopic surgery.

Following a series of preclinical studies, the first live human application of robotic surgery in the head and neck for excision of base of tongue tumours was described in 2005 [2]. The acronym 'TORS' (TransOral Robotic Surgery) was thereby established in the medical literature, which has now been universally adopted.

Transoral Robotic Surgery (TORS)

TORS capitalised on the presence of the oral cavity as an access point for Natural Orifice Transluminal Endoscopic Surgery (NOTES), thus providing access to the pharynx, parapharyngeal space and larynx, without the morbidity of open surgery or the limitations associated with previously described transoral approaches, namely Transoral Laser Microsurgery (TLM).

Robotic technology overcomes the limitations of traditional endoscopic surgery. The dual channel endoscope offers a 3-D magnified view of the operative field, permitting depth perception compared to a 2-D view with conventional single-channel endoscopy. Moreover, wristed robotic instruments can operate with 7 degrees of freedom. This facilitates precise tissue manipulation within the confines of the oral cavity. Finally, surgical dexterity is enhanced by the tremor-filtering and motion-scaling features of the da Vinci® robotic system [3].

Oropharyngeal cancer constitutes the commonest application of TORS. It represents an increasingly common cancer affecting younger patients as a result of Human Papilloma Virus infection (primarily the HPV-16 genotype). This has been traditionally managed with 'organ preservation' treatments in an attempt to avoid the morbidity of open surgery. However, the toxicity and complications associated with primary chemoradiotherapy are often severe with substantial impact on both function and Quality of Life (QoL). TORS minimises the functional problems associated with chemoradiation through a de-escalation approach that is customised to the patient. This has created a paradigm shift in head and neck cancer treatment, and introduced the concept of 'functional organ preservation surgery' [4].

In just over a decade, TORS has evolved from proof-of-concept to standard-of-care in high volume robotic centres, with FDA approval for both benign and malignant diseases being given in 2009 [5]. Although indications for TORS initially involved base of tongue neoplasms, increasing clinical experience combined with preclinical studies on animals and cadavers, have rapidly expanded its applications [6].

Currently, TORS is a valuable treatment modality not only for tumours of the oropharynx, but also of the hypopharynx [7], parapharyngeal space [8] and larynx [9]. More recently, TORS has been used in managing carcinoma of unknown primary [10] and head and neck reconstruction, both in terms of free-flap positioning and microvascular anastomosis for the repair of large oropharyngeal defects following TORS resection [11].

There is an increasing body of evidence supporting the role of TORS in the treatment of a number of head and neck cancers. However, this mainly relates to case series and retrospective matched-cohort studies. There are 3 multicenter Randomised Controlled Trials (RCTs) currently under way: PATHOS, a UK-based study (HPV positive oropharyngeal cancer), the US RTOG 1221 (HPV negative oropharyngeal cancer), and finally the Canadian ORATOR study (early-stage oropharyngeal cancer).

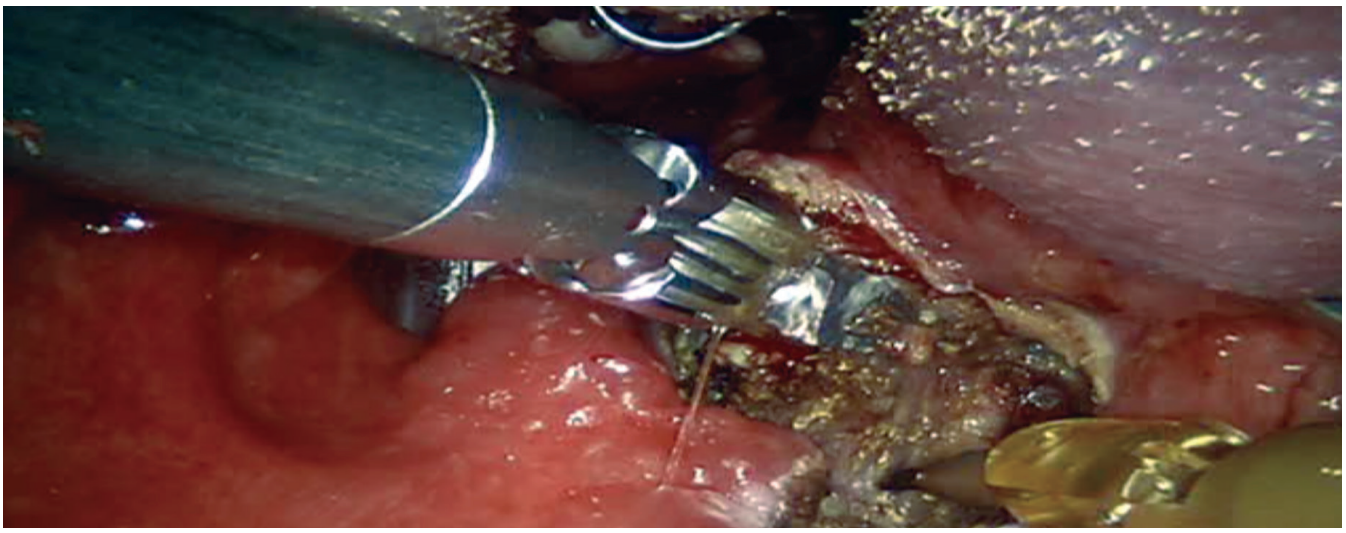
Transaxillary Robotic Surgery

Application of transaxillary robotic surgery for the treatment of thyroid cancer was first described in 2009 [12]. Following this, robotic thyroidectomy increased in popularity, with thousands of patients been treated for differentiated thyroid cancer (primarily of the papillary type) with excellent outcomes [13].

Both thyroidectomy (lobectomy, isthmusectomy, and/or total thyroidectomy) and concomitant neck dissection (central and/or lateral compartment including modified radical neck dissection) can be performed through the transaxillary route using the da Vinci® surgical robot with excellent functional and oncological outcomes [14].

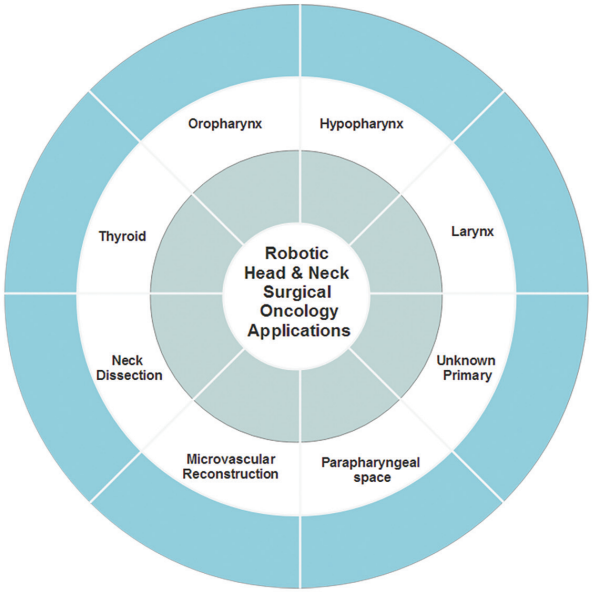
It is important, however, to recognise that most of the evidence supporting robotic thyroidectomy originates from South Korea where the majority of studies have taken place. Moreover, there are no RCTs on the subject. The uptake in the Western World has been particularly low, with robotic thyroidectomy accounting for <1% of total thyroid surgical volume in both the UK and US [15].

Several reasons have been implicated in this



TORS right oropharyngectomy

TORS supraglottic laryngectomy



discrepancy. These include cultural differences (negative connotation associated with horizontal neck scar in the Far East not present in Western societies) and anthropometric differences (patients from the Far East are on average smaller and thinner than their Western counterparts, facilitating transaxillary access). There are also differences in terms of the incidence and size of thyroid nodules on presentation (there is a national thyroid cancer screening programme in South Korea leading to nodules and thyroid malignancy being picked up at a higher rate and earlier stage) as well as incentives for surgeons (in the Korean healthcare system, remuneration for the robotic approach is double that of the endoscopic approach and quadruple that for open thyroidectomy, whereas in Western healthcare systems the route used for access has no impact on remuneration; instead, it is the extent of surgery that dictates reimbursement [15].

As a result, the evidence for robotic thyroidectomy (and/or neck dissection) in the treatment of benign and malignant disease should be interpreted with caution.

The Future

The da Vinci® surgical robot was not originally designed for head and neck surgery, as previously discussed. Thus there is room to develop a bespoke robot for transoral use.

The first step involves the design, manufacturing and trialing of miniaturized flexible robots, which will permit access to areas of the head and neck that are not currently possible (or limited) with existing robotic surgical techniques. Such areas include the glottic and subglottic larynx, trachea, nasopharynx, skull base (sellar and parasellar regions) and infratemporal fossa.

Moreover, robotic surgery could be combined with other existing technologies, like augmented reality or narrow-band imaging to enhance real-time intraoperative navigation, improving the precision of robotic resection and optimizing patient safety.

Another important factor that will determine the future of robotic head and neck surgical oncology is cost. This relates to the purchase, consumables and maintenance costs, which are currently prohibitive for most patients, insurers and healthcare systems. This is facilitated by the Intuitive Surgical® monopoly in the robotic surgery market. However, this

will change as multinational medical device companies, such as Medtronic® (Minneapolis, MN, US), Medrobotics® (Raynham, MA, US), and the Johnson & Johnson® (New Brunswick, NJ, US)-Google® (Mountain View, CA, US) partnership, enter the robotic surgery arena. Market competition can be expected to drive down costs, making robotic surgical technology more widely available.

The results of several ongoing multicentre RCTs from both the UK and North America are awaited with interest in order to define the exact role and advantages of robotic surgical technology over 'established' treatments for head and neck cancer. TORS does have the potential to offer important advantages over both chemoradiotherapy (dose de-escalation or even as single modality therapy) and traditional open surgery (avoidance of incisions and minimising disruption of extrinsic pharyngeal muscles), but like with all surgical interventions, this holds true in carefully selected patients in the context of high-volume surgeons forming part of multidisciplinary teams within specialised centres.

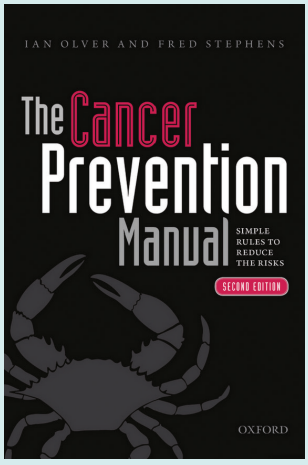
REFERENCES

1. da Vinci® Surgery: Minimally Invasive Surgery [http://www.davincisurgery.com]
2. O'Malley BW Jr, Weinstein GS, Snyder W, et al. *Transoral robotic surgery (TORS) for base of tongue neoplasms.* Laryngoscope 2006; 116(8):1465-72.
3. Moorthy K, Munz Y, Dosis A, et al. *Dexterity enhancement with robotic surgery.* Surg Endosc 2004; 18(5):790-5.
4. Bhayani MK, Holsinger FC, Lai SY. *A shifting paradigm for patients with head and neck cancer: transoral robotic surgery (TORS).* Oncology (Williston Park) 2010; 24(11):1010-1015.
5. Van Abel KM, Moore EJ. *The rise of transoral robotic surgery in the head and neck: emerging applications.* Expert Rev Anticancer Ther 2012; 12(3):373-80.
6. Arora A, Kotecha J, Acharya A, et al. *Determination of biometric measures to evaluate patient suitability for transoral robotic surgery.* Head Neck 2015; 37(9):1254-60.
7. Sims JR, Robinson NL, Moore EJ, et al. *Transoral robotic medial hypopharyngectomy: Surgical technique.* Head Neck 2016; 38 Suppl 1:E2127-9.
8. O'Malley BW Jr, Quon H, Leonhardt FD, et al. *Transoral robotic surgery for parapharyngeal space tumors. ORL* J Otorhinolaryngol Relat Spec 2010; 72(6):332-6.
9. Mendelsohn AH, Remacle M, Van Der Vorst S, et al. *Outcomes following transoral robotic surgery: supraglottic laryngectomy.* Laryngoscope 2013; 123(1):208-214.
10. Mehta V, Johnson P, Tassler A, et al. *A new paradigm for the diagnosis and management of unknown primary tumors of the head and neck: a role for transoral robotic surgery.* Laryngoscope 2013; 123(1):146-51.
11. Selber JC. *Transoral robotic reconstruction of oropharyngeal defects: a case series.* Plast Reconstr Surg 2010; 126(6):1978-87.
12. Kang SW, Jeong JJ, Nam KH, et al. *Robot-assisted endoscopic thyroidectomy for thyroid malignancies using a gasless transaxillary approach.* J Am Coll Surg 2009; 209(2):e1-7.
13. Lee S, Ryu HR, Park JH, et al. *Excellence in robotic thyroid surgery: a comparative study of robot-assisted versus conventional endoscopic thyroidectomy in papillary thyroid microcarcinoma patients.* Ann Surg 2011; 253(6):1060-1066.
14. Lee J, Yun JH, Nam KH, et al. *Perioperative clinical outcomes after robotic thyroidectomy for thyroid carcinoma: a multicenter study.* Surg Endosc 2011; 25(3):906-912.
15. Arora A, Garas G, Sharma S, et al. *Comparing transaxillary robotic thyroidectomy with conventional surgery in a UK population: A case control study.* Int J Surg 2016; 27:110-7.

BOOK REVIEW

The Cancer Prevention Manual – Simple rules to reduce the risks

Ian Olver and Fred Stephens, Second Edition. Published by: Oxford University Press. ISBN: 978-0-19-871985-4. Price: £12.99.



This is a small manual of 91 pages written by two eminent Australian Professors. The book is aimed at the general public in order to present the message of cancer prevention clear and accessible, rather than as a text for medical professionals. With this in mind I found that the text was easy to comprehend and the language used clear and avoided the use of jargon. Technical terms were explained in the text rather than being presented in a glossary; however I found that a glossary would have been helpful as an aid for definitions. Simplistic line -drawings are presented as illustrations and are effective in conveying the message. The information in the manual is evidenced based.

The book comprises five chapters; Chapter 1 – What is cancer? This explains the concept of mitotic growth in layman terms and focuses the reader on how cancer may be prevented by one making life style choices.

Chapter 2 – What causes cancer? This is explained by the fact that genetic mutations are responsible for instructing abnormal growth. I feel that an explanation of Knudson's hypotheses may have helped in the understanding of heritability in the complex development of oncogenesis. The authors have discussed inherited gene mutations as cause of cancers before that of sporadic cancers: I feel that much more emphasis should have been placed on the formation of sporadic cancers, especially as these are likely to be influenced by making the lifestyle changes such as stopping cigarette smoking, thereby reducing the risks.

Chapter 3 – Lifestyle changes that prevent cancer. This chapter looks at the modifiable risk factors for cancer for instance smoking, diet, exercise, obesity and alcohol intake. Sun protection is discussed in detail as expected for an Australian readership; however this issue is becoming increasingly more important in Britain and Europe. Tips on how to stop smoking and how to protect oneself from the harmful effects of the sun are discussed in a helpful way.

Chapter 4 – Risk factors and the prevention of specific cancers. This chapter examines the causes of the top 20 causes of cancer worldwide and explores the evidence available to prevent them. Chapter 5 – Research into cancer risk explains the need of and how to perform clinical trials. The bibliography presents information suitable for the lay person on international cancer websites. In summary this is a useful and easy to read guide on cancer prevention.

Dr Karin Baria, Retired Consultant Oncologist.

Diet and Cancer Prevention

Pamela A. Popper, PhD, ND,
Naturopath,
Executive Director,
Wellness Forum Health,
Worthington, OH, USA.

Correspondence to:
E: pampopper@msn.com

While billions of dollars have been spent on initiatives like The War on Cancer, the incidence of cancer continues to increase, along with the death rate for many of its forms. The National Cancer Institute estimated that 1,685,210 new cases of cancer would be diagnosed in the U.S. in 2016 and that ~595,690 people would die, which means an average of 1,632 cancer deaths per day [1]. This is an increase from 2009, when it was estimated that 1,479,350 Americans would be diagnosed with cancer, and 562,340 would die, an average of 1,500 cancer deaths per day [2].

Over-diagnosis is a factor in these statistics. Research has shown that PSA testing and mammography, for example, have resulted in the diagnosis of many "pseudo-cancers", which really are not cancers requiring treatment, yet they are treated as if they are cancers [3-7]. But even after accounting for these inflated statistics, cancer incidence continues to increase.

Some of the most significant contributors to cancer risk are diet and lifestyle choices, weight, and inflammation, all of which can be modified to reduce risk. The best option is to prevent cancer, and research shows that most cancers and deaths from cancer are preventable [8].

Weight Gain Increases the Risk

One of the leading causes of many types of cancer is being overweight. A review of over one thousand studies conducted by the International Agency for Research on Cancer showed that being overweight or obese increases the risk for at least 13 types of cancer [9]. According to Dr Graham Colditz, chairman of the research group, these 13 cancers represent 42% of all cancer diagnoses. He says that weight status is an even more important factor than smoking in terms of cancer risk, and that obesity should be at the top of the list of risk factors regarding cancer prevention [10].

While many factors contribute to weight gain and obesity, diet is the most important. It is easier to gain weight by eating foods high in calories and fat, e.g. beef, cheese and pastries. And it is easier to lose weight by eating a plant-based diet that includes lower calorie intake, like fruits and vegetables.

Inflammation Increase Progression

Inflammation increases the risk of cancer and can also accelerate its progression. Cancers often develop at sites where infection, chronic irritation or inflammation have occurred [11]. Taking colon cancer as an example, >35% of Americans develop polyps due to changes in the mucosal layer that protects the lining of the colon [12]. The primary cause of these changes is over-consumption of animal foods. Sulphur-containing amino acids in animal protein increase the production of hydrogen sulfide. This noxious substance reduces mucus production, leaving the lining of the colon vulnerable to irritation, which in turn can lead to the formation of polyps [13] – the greater the irritation, the bigger the polyps become, and the higher the risk they will develop into colon cancer.

Ultimately Diet Has A Powerful Influence on Cancer Risk

In addition to being high in protein, animal foods are high in fat. Higher fat intake increases the production of bile acids, which also irritate the colon. Thus a diet lower in fat and higher in fiber is protective because it reduces bile acid production and helps the body to eliminate bile acids more quickly [14].

Many studies have shown a relationship between diet and the risk of colon cancer. In 1971, Dr Denis Burkitt reported that African blacks eating a plant-based diet had a lower risk of death from colon cancer than African whites eating a Westernized diet [15]. Numerous studies have shown that eating animal foods increases the risk of colon cancer in a dose-dependent manner – the more animal foods consumed, the higher the risk [16-18]. On the other hand, research shows that eating a higher fiber diet reduces the risk of colon cancer [19-21], and that vegetarians are ~40% less likely to develop colon cancer compared to meat eaters [22,23].

Another way in which high intake of animal foods contributes to increased inflammation and an increased risk of cancer is that they contain concentrated amounts of arachidonic acid, which can increase inflammation levels through numerous pathways [24]. Thus, reducing or eliminating animal foods can significantly reduce inflammation and cancer risk.

Obesity also contributes to inflammation because fat cells produce inflammatory cytokines and similar molecules [25]. Adopting a low-fat plant-based diet usually results in weight loss, which in turn can reduce inflammation. Plant-based diets are also high in fibre, which reduces inflammation by interacting with gut bacteria [26].

Plant-Based Diets Lower the Risk

Well-structured plant-based diets reduce the risk of cancer in several other ways. In addition to fibre, plant foods contain concentrated levels of antioxidants that can counteract the oxidative

stress caused by poor diets, inflammation and infection. These diets also call for elimination of cancer-promoting foods, like dairy products, which increase IGF-1 levels – a known risk for cancer [27-31].

The role of IGF-1 in cancer development has been known for some time. In 2002, one study showed that higher plasma IGF-1 levels were associated with a higher incidence of prostate cancer, and higher levels of IGF-1 binding proteins were inversely associated [32]. Others have shown a relationship between IGF-1 levels and breast, colorectal, lung, thyroid, bone, brain and ovarian cancers [33-37]. Lower levels of IGF-1 have been associated with longer survival of cancer patients [38].

The good news is that IGF-1 levels are related to diet, and dietary changes can lower plasma levels. Higher protein intake is associated with higher plasma levels of IGF-1, and lower protein intake with lower plasma levels, lower incidence of cancer, and lower mortality of people under age 65 [39]. This relationship between lowered protein intake and lower plasma IGF-1 levels has been reported [40], particularly animal protein [41]. Milk and whey protein intake increase IGF-1 levels significantly [42,43], which explains why dairy intake is associated with so many types of cancer.

Obstacles to Change

The idea that diet can prevent cancer is not a new one. As long ago as 1892, an article in Scientific American reported that "cancer is most frequent among those branches of the human race where carnivorous habits prevail" [44]. So why don't more people eat optimal diets in order to reduce their risk of cancer, and why aren't more doctors promoting plant-based nutrition for cancer prevention?

Some of the most significant contributors to cancer risk are diet and lifestyle choices, weight, and inflammation, all of which can be modified to reduce risk

Medical training is one contributing factor. US doctors receive almost no training in nutrition. According to a 2015 study, only 27% of US medical schools offer the 25 hours of nutrition education currently recommended. The average is 19.6 hours of nutrition classes during 4 years of medical school, i.e. <1% of total lecture hours. Most of this consists of biochemistry, not practical information about diets or food-related decision-making [45].

Another issue is that, while many doctors recognize the need for nutrition education, there are few incentives for providing it. For example, the current licensure exam evaluates "biochemical knowledge and information relating to nutritional deficiencies," but does not test for knowledge or skills needed for discussing diet and lifestyle changes with patients. Board certifications, including those for internal medicine and cardiology, do not require demonstration of expertise in nutrition.

Another very important issue is the tendency of physicians to assume that patients are not interested in dietary change or working to improve their health. A common misconception is that people only want "quick fixes" for their health issues. But "quick fixes" – meaning drugs and procedures – are usually the only choices offered to patients. Most people are not told that diet and lifestyle habits can prevent or resolve their health issues, and there is no multi-billion dollar media campaign promoting nutrition as an effective strategy for addressing health conditions.

It is clearly time for several changes, which include nutrition education as a part of medical training, and demonstration of nutrition knowledge as a criteria for licensure. Doctors should be taught how to converse with patients so that all options for prevention and treatment are discussed, including improved diet. And medical practices should include nutrition and lifestyle education for their patients. These changes will require time, commitment and resources. But our only hope for winning the war on cancer is to invest more effort in preventing it.

REFERENCES

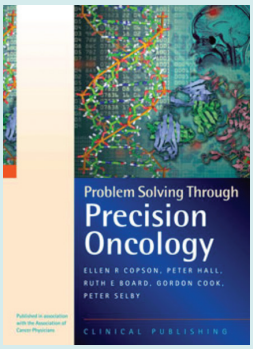
1. Cancer Statistics https://www.cancer.gov/about-cancer/understanding/statistics accessed 12.25.2016
2. American Cancer Society Cancer Facts and Figures 2009 Atlanta Georgia 2009.
3. Kobayashi T, Nichizawa K, Mitsumori K, et al. *Detection of prostate cancer in men with prostate-specific antigen levels of 2.0 to 4.0 ng/ml equivalent to that in men with 4.1 to 10.0 mg/ml in a Japanese population.* Urology 2004; Apr;63(4):727-31.
4. Coldman A, Phillips N, Pickles T. *Trends in prostate cancer incidence and mortality; an analysis of mortality change by screening intensity.* CMAJ 2003; Jan 7;168(1):31-5.
5. US Preventive Services Task Force Screening For Breast Cancer: U.S. *Preventive Services Task Force Recommendation.* Ann Intern Med November 17, 2009;151:1716-26.
6. Esserman L, Shieh Y, Thompson I. *Rethinking Screening for Breast Cancer and Prostate Cancer.* JAMA 2009;302(15):1685-92.
7. Berrington de Gonzalez A, Berg C, Visvanathan K, et al. *Estimated Risk of Radiation-Induced Breast Cancer From Mammographic Screening for Young BRCA Mutation Carriers.* J Natl Cancer Inst 2009; 101: 205-209.
8. Song M, Giovannucci E. *Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States.* JAMA Oncol. Published online May 19, 2016. doi:10.1001/jamaoncol.2016.0843
9. Lauby-Secretan B, Scoccianti C, Loomis D, et al. *Body Fatness and Cancer — Viewpoint of the IARC Working Group.* NEJM 2016; August; 375 (8): 79.
10. Bakalar N. *Obesity Is Linked to at Least 13 Types of Cancer.* New York Times August 24, 2016.
11. Coussens L, Werb A. *Review article: Inflammation and Cancer.* Nature 19 December 2002;420;860-7.
12. Midgley R, Kerr D. *Colorectal Cancer.* Lancet 1999; Jan;35(9150):391-9.
13. Tuan J, Chen Y. *Dietary and Lifestyle Factors Associated with Colorectal Cancer Risk and Interactions with Microbiota: Fiber, Red or Processed Meat and Alcoholic Drinks.* Gastrointest Tumors 2016;3:17-24.
14. Ajouz H, Mukherju D, Shamseddine A. *Secondary bile acids: an underrecognized cause of colon cancer.* World J Surg Oncol 2014; 12: 164.
15. Burkitt D. *Epidemiology of cancer of the colon and rectum.* Cancer 1971; Jul;28(1):3-13.
16. Giovannucci E, Rimm E, Stampfer M, et al. *Intake of fat, meat, and fiber in relation to risk of colon cancer in men.* Cancer Res 1994;54(9):2390-7.
17. Willett W, Stampfer M, Colditz G, et al. *Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women.* NEJM 1990;323:1664-72.
18. World Cancer Research Fund. *Food, nutrition, physical activity, and the prevention of cancer: A global perspective.* American Institute of Cancer Research. Washington, DC:2007.
19. Reddy B. *Role of dietary fiber in colon cancer: an overview.* Am J Med 1999 ;Jan 25;106(1A):16S-19S.
20. MacLennan R, Macrae F, Bain C, et al. *Randomized trial of intake of fat, fiber, and beta carotene to prevent colorectal adenomas.* J Natl Cancer Inst 1995; Dec 6;87(23):1760-6.

21. Howe G, Benito E, Castellato R et al. *Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence form the combined analysis of 13 case-control studies.* J Natl Cancer Inst 1992; Dec 16;84(24):1887-96.
22. Chang-Claude J, Frentzel-Beyme R, Eilber U. *Mortality patterns of German vegetarians after 11 years of follow-up.* Epidemiology 1992;3:395-401.
23. Chang-Claude J, Frentzel-Beyme R. *Dietary and lifestyle determinants of mortality among German vegetarians.* Int J Epidemiol 1993;22:228-36.
24. Samuelsson B. *Arachidonic acid metabolism: role in inflammation.* Z Rheumatol 1991;50 Suppl 1:3-6.
25. Greenberg A, Obin M. *Obesity and the role of adipose tissue in inflammation and metabolism.* Am J Clin Nutr Feb 2006;83(2):461S-465S.
26. Kuo SM. *The Interplay Between Fiber and the Intestinal Microbiome in the Inflammatory Response.* Adv Nutr January 2013;4:16-28.
27. Wei E, Ma J, Pollack M et al. *Prospective Study of C-Peptide, Insulin-like Growth Factor-I, Insulin-like Growth Factor Binding Protein-1, and the Risk of Colorectal Cancer in Women.* Cancer Epidemiol Biomarkers Prev 2005; April: 14; 850.
28. Birmann B, Tamimi R, Giovannucci E. *Insulin-like growth factor-1- and interleukin-6-related gene variation and risk of multiple myeloma.* Cancer Epidemiol Biomarkers Prev 2009; Jan;18(1):282-8.
29. Kaaks R, Johnson T, Tikk K et al. *Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status-A prospective study within the EPIC cohort.* Int J Cancer 2014; Jun 1;134(11):2683-90.
30. Cao H, Wang G, Meng L et al. *Association between circulating levels of Igf-1 and IGFPB-3 and lung cancer risk: a meta-analysis.* PLoS One 2012;7(11):e49884.
31. Schmidt J, Allen N, Almquist M et al. *Insulin-like growth factor-1 and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition.* Cancer Epidemiol Biomarkers Prev 2014; Jun;23(6):976-85.
32. Chan J, Stampfer M, Ma J et al. *Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer.* J Natl Cancer Inst 2002; Jul 17;94(14):1099-1106.
33. Wei E, Ma J, Pollack M et al. *Prospective Study of C-Peptide, Insulin-like Growth Factor-I, Insulin-like Growth Factor Binding Protein-1, and the Risk of Colorectal Cancer in Women.* Cancer Epidemiol Biomarkers Prev 2005; April: 14; 850.
34. Birmann B, Tamimi R, Giovannucci E. *Insulin-like growth factor-1- and interleukin-6-related gene variation and risk of multiple myeloma.* Cancer Epidemiol Biomarkers Prev 2009; Jan;18(1):282-8.
35. Kaaks R, Johnson T, Tikk K et al. *Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status-A prospective study within the EPIC cohort.* Int J Cancer 2014; Jun 1;134(11):2683-90.
36. Cao H, Wang G, Meng L et al. *Association between circulating levels of Igf-1 and IGFPB-3 and lung cancer risk: a meta-analysis.* PLoS One 2012;7(11):e49884.
37. Schmidt J, Allen N, Almquist M et al. *Insulin-like growth factor-1 and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition.* Cancer Epidemiol Biomarkers Prev 2014; Jun;23(6):976-85.
38. Milman S, Atzmon G, Huffman D, et al. *Low inuslin-like growth factor-1 level predicts survival in humans with exceptional longevity.* Aging Cell 2014; Aug;13(4):769-71.
39. Levine M, Suarez J, Brandhorst S et al. *Low protein intake is associated with a major reduction in IGF-1, cancer and overall mortality in the 65 and younger but not older population.* Cell Metabol 2014; Mar 4;19(3):407-414.
40. Fontana L, Weiss E, Villareal D, et al. *Long-term effects of calorie or protein restriction on serum IGF-1 and IGFPB-3 concentration in humans.* Aging Cell 2008; Oct;7(5):681-7.
41. Michaelson K, Greer F. *Protein needs early in life and long-term health.* Am J Clin Nutr 2014; Mar;99(3):718S-722S.
42. Qin L, He K, Xu J. *Milk consumption and circulating insulin-like growth factor-1 level: a systematic literature review.* Int J Food Sci Nutr 2009;60 Suppl 7:330-40.
43. Zhu K, Meng X, Kerr D et al. *The effects of a two-year randomized controlled trial of whey protein supplementation on bone structure, IGF-1, and urinary calcium excretion in older postmenopausal women.* J Bone Miner Res 2011; Sep;26(9):2298-306.
44. Scientific American 1892; January. https://is.gd/zMH4T3
45. Eisenberg D, Burgess J. Nutrition Education in an Era of Global Obesity and Diabetes: Thinking Outside the Box. Academic Medicine 2015; July;90(7):854-60.

BOOK REVIEW

Problem Solving Through Precision Oncology

Ellen R Copson, Peter Hall, Ruth E Board, Gordon Cook, Peter Selby. Published by: Clinical Publishing. ISBN: 978-1-84692-111-7. Price: £39.95.



This 214 page book is published in association with the Association of Cancer Physicians. The majority of contributors are UK based and the book reflects medical oncology practice within the UK. This book provides a practical review of the latest progress of a fast moving field and is especially recommended for the Oncology Trainee; however other members of the multidisciplinary team will find it a useful reference source.

Oncology practice has changed vastly over recent decades and many of the developments and successes in patient treatment relate to personalised medicine and treatments directed solely to those likely to derive benefit. Precision oncology refers to the implementation of specific therapies from diagnosis at a molecular level through to treatment in the clinic.

This book is divided into two sections. Section One: Perspectives. This includes 15 chapters which examine and discuss the techniques available to identify features of individual malignancies which enable specific treatments to be employed. For instance the use of biomarkers such as AFP, B-HCG in the management of testicular cancer, and the testing of cancer susceptibility genes e.g BRCA 1/2 in families with a high incidence and early onset of breast/ ovarian cancers. The development of in vitro diagnostics essential for diagnosis, treatment selection and monitoring of malignancies is reviewed along with the concept of conducting clinical trials in the hope of improving outcomes.

Section Two: Case Studies. This includes 21 chapters detailing the management of patients with specific conditions, which are relevant to a wide ranging clinical practice. A case history is provided followed by several thought provoking questions about the patient's management.

The answers to the questions are discussed in detail thereby providing the reader with the latest information about the subject, citing trial data and references. Finally a section Conclusions and learning points presents essential information in a bullet point style. A list of references is provided at the end of each chapter.

I found the cases interesting and informative: breast cancer with BRCA mutation, colorectal, malignant melanoma, GIST, ovarian, NSCLC and lymphoma all with abnormal genetic faults. These case studies demonstrate that when new treatments used appropriately or with precision how the patient's management and hopefully survival rates are improved. I feel that a chapter on the treatment of metastatic renal cell carcinoma with cytokines would be helpful.

In summary I found this book easy to read on the eye, it was well laid out with lots of clear diagrams and tables. In addition the topics were wide ranging making it suitable for oncology trainees and other members of the oncology team.

Dr Karin Baria, Retired Consultant Oncologist.

Latest developments on products and services from the industry. To have your news included contact Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

Beating Bowel Cancer holds their first Midlands Patient Day

The charity Beating Bowel Cancer held their first Midlands Patient Day at the Charles Hastings Education Centre, Worcester Royal Hospital, on Saturday 8 April 2017. The free event was a great opportunity for patients and their families to take part in interactive workshops on the physical and emotional effects of bowel cancer, practical advice on healthy living during and after treatment, a keep fit session, a carers' only session and the latest advances in surgery and treatment.

The event was organised with great support from the colorectal nursing team of Worcestershire Acute Hospitals NHS Trust, which includes hospitals in Worcester, Redditch and Kidderminster. Their stoma nurses, dieticians and chemotherapy nurses were on hand all day with reassurance and advice.

Presentations given at the event are available to download on the Patient Day page at beatingbowelcancer.org

For further information:
E: patient@beatingbowlecancer.org
W: www.beatingbowelcancer.org or
@bowelcancer

Varian Medical Systems establishes direct operation in South Africa

Varian Medical Systems is establishing a direct sales and service operation in South Africa to better serve the growing cancer population. Varian's South African entity will be based in Johannesburg.

"It is now time for Varian to get closer to the market and provide direct sales and service support for the growing number of oncology departments in South Africa that provide treatments using our radiotherapy equipment and software," says Jean-Luc Devleeschauwer, president of Varian's operations in Europe, the Middle East and Africa. "We have always intended to operate directly in South Africa and we now feel the time is right to do so."

Varian has historically sold and serviced its technology-leading radiotherapy systems to South African hospitals via a Johannesburg-based distributor, Tecmed Africa, but now intends to sell and service its systems directly.

Varian has installed more than 100 radiotherapy systems across Africa over the past 25 years, including 30 in South Africa. The company has also launched its 'Access to Care' educational program in the country in cooperation with Groote Schuur Hospital, providing training for radiation oncologists, medical physicists and radiotherapy therapists from across the African continent.

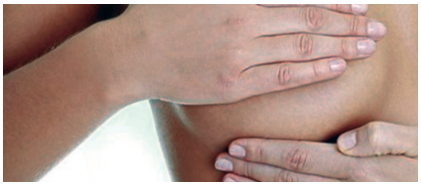
For more information visit www.varian.com and @VarianMedSys

New evidence highlights significant impact of Oncotype DX® test

Genomic Health has unveiled data providing further evidence that the Oncotype DX® breast cancer test accurately predicts outcomes and has important clinical utility in patients whose breast cancer has spread to their lymph nodes.

The test, already widely used for node-negative patients, uncovers the unique footprint of each patient's tumour and generates a Recurrence Score® which predicts the likelihood that the patient's cancer will return and therefore the potential benefit of chemotherapy. Findings from 385 patients presented at the 15th St Gallen International Breast Cancer Conference suggest the test changes clinical decisions for 43% of node-positive patients too, reducing the need for chemotherapy.

Steven Shak, chief scientific officer, Genomic Health, said: "These latest presentations



clearly highlight the impact of Oncotype DX in reducing chemotherapy usage and driving more cost-effective treatment, as well as its value in providing doctors with confidence that their patients will receive the quality care they deserve."

For any further information contact Genomic Health Customer Support team: T: +44 020 3031 8087 F: +44 020 7067 9405 E: europeansupport@genomichealth.com or @Genomic

FDA clearance for British family developed scalp cooler

A scalp cooling technology that was developed by a British family to reduce hair loss in breast cancer patients undergoing chemotherapy, has been given clearance from the U.S. Food and Drug Administration (FDA).

The concept behind the Paxman Scalp Cooling System came when the mother of four, Sue Paxman, experienced first-hand the trauma of chemotherapy-induced hair loss.

The Company has since been on a personal journey to ensure Sue's legacy lives on by helping women around the globe minimise hair loss and contribute to their quality of life.

"It is estimated that 8% of patients actually refuse chemotherapy because they do not want to lose their hair," explains CEO Richard Paxman.

"After experiencing this first hand, we have been determined to change this, and help minimise hair loss in women undergoing chemotherapy, positively contributing to their overall health and recovery."

The Paxman scalp cooler will be showcased at the American Society of Clinical Oncology (ASCO) on booth 25157.

For more information visit www.paxmanscalpcooling.com @scalpcooling

State government of North-Rhine Westphalia grants research funds to Varian

North-Rhine Westphalian minister for the economy Mr Garrelt Duin today awarded Varian Medical Systems Particle Therapy GmbH research funds amounting to about 10 million Euros. The funding will be used for the further development of proton therapy.

Proton therapy provides a highly targeted treatment for cancer patients and offers specific advantages for paediatric patients. This advanced non-invasive therapy helps to reduce side effects.

The funding comes from the European Regional Development Fund (EFRD/EFRE). The investment will be used to make the technology accessible to a larger group of patients around the globe.

State Minister Garrelt Duin (2nd from right) with employees of Varian Particle Therapy in Troisdorf, Germany

"This is a good day for North Rhine-Westphalia." states minister Duin during his visit to Varian in Troisdorf, Germany. "In addition to significantly improving the treatment options for tumours, this funding is a great opportunity for cooperation between science and industry in the high-tech location of North-Rhine Westphalia. Varian will help equip the global health market from here."

"Through these research and development projects we will cooperate with universities, colleges and partner companies. Using the concept of 'Open-Innovation' we thus want to lay the foundations for the development of ground-breaking technologies and contribute to the improvement of patient care," emphasizes Dr Wolfgang Kaissl, managing director of Varian Particle Therapy in Germany.

For more information visit www.varian.com and @VarianMedSys

NEW Fluorescent Peptide Imaging application of PXi System allows German researchers to easily detect leukaemia associated proteins

Syngene's PXi multi-application imager is being used by scientists at the prestigious Freie Universtät Berlin for the new application of imaging fluorescent peptides on Western blots. The system provides the researchers with a simple, sensitive method to detect cancer-linked transcription factors.

In the Institute for Pharmacy at the Freie Universtät Berlin, scientists are using the PXi imaging system for imaging a peptide labelled with 5-carboxyfluorescein to fish out key interacting protein partners to essential transcription factors. This drug discovery research may contribute to finding druggable targets for treating leukaemia and other cancers.

Ee Lin Wong, a PhD student added: "We chose the PXi because the system is compact but more sensitive than film. This saves time as we can detect the proteins we're looking for without having to keep repeating our fluorescent blots or use extra X-ray film. The software is very fast and downloads images we can save to a USB stick in a format we can easily analyse and transfer into a file at exactly the right specifications for publication. This allows us to submit good quality figures more rapidly to scientific journals and is a great feature."

For Further Information contact: Jayne Arthur, Syngene T: +44(0) 1223 727123 E: jayne.arthur@syngene.com or visit: www.syngene.com/pxi-pxi-touch

Taking the strain out of cancer diagnostics

Rainin electronic pipettes are helping California-based Clarient Diagnostic Services, Inc. to provide cancer diagnostic testing. Flow cytometry supervisor Brian Ngo explained: "Our laboratory uses flow cytometry to detect specific biomarkers that help to diagnose leukaemia, and this involves pipetting microliter volumes of antibodies and samples. When you are doing a lot of pipetting, user comfort is very important and so we decided to invest in electronic pipettes."

"We looked at the various options available, and chose Rainin E4 XLS single channel pipettes because they are ergonomically designed and very easy to hold. They are also quite intuitive to use with the benefit of a large LCD screen. There are advantages from a GLP perspective too, as the programmed volume ranges can be password protected and particular features locked down or hidden. The pipettes are very dependable and, as they can operate accurately over a range of volumes we have been able to reduce the number of pipettes in the lab from over 100 to about 10, significantly decreasing our calibration costs."

For more information contact: Mettler Toledo Rainin T +1 800 472-4646 W: www.mt.com/rainin @MettlerToledoPR

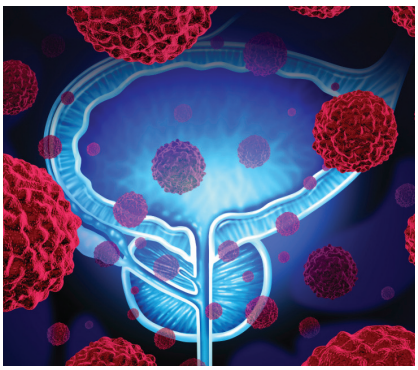
Royal Surrey introduces rectal sparing hydrogel

St Luke's Cancer Centre, part of the Royal Surrey County Hospital NHS Foundation Trust, has transformed the way it delivers prostate brachytherapy with the use of SpaceOAR® from Oncology Systems Limited. The hydrogel, placed between the prostate and rectum, has enabled the Cancer Centre to provide prostate brachytherapy to patients with cases that would usually have been considered a contraindication or those who have previously received external beam radiotherapy (EBRT). With the use of SpaceOAR, the Centre can minimise the risk of radiation to the rectum, enabling it to offer life-changing brachytherapy treatment to a greater number of men.

SpaceOAR hydrogel is injected as a liquid between the prostate and rectum under ultrasound guidance. Insertion takes just a few minutes and negates the need for additional operations and general anaesthetic. Once injected, the liquid solidifies into a hydrogel that creates a temporary space between the prostate and rectum. The intent is to position the anterior rectal wall away from the prostate during radiotherapy and reduce the radiation dose delivered to the anterior rectum. The hydrogel maintains space for about three months and then liquefies, allowing it to be naturally absorbed by the body in about six months.

Professor Stephen Langley, Clinical Director for Urology at St Luke's Cancer Centre comments, "SpaceOAR acts as a natural extension to our existing brachytherapy treatment and in future, it would be hard to not justify using it."

For further information visit www.osl.uk.com or T: +44 (0)1743 462694 E: enquiry@osl.uk.com @OSL1



Almac Group Announces Publication of Prostate Cancer Metastatic Assay Validation

Almac Group's Diagnostics business unit today announced the Journal of European Urology has published results relating to its Prostate Cancer Metastatic Assay. The publication demonstrates the assay can be used to analyse primary prostate cancer FFPE samples to identify a molecular subgroup with a high risk of developing distant metastases. The assay therefore has the potential to guide the choice of therapy for patients presenting with primary prostate cancer.

Professor Richard Kennedy, MD, PhD, VP and Medical Director, Almac Diagnostics and McClay Professor in Medical Oncology, Queen's University Belfast commented "An unbiased discovery approach was used to identify a molecular subtype of primary prostate cancer that demonstrated metastatic biology. This approach has created a very robust assay with excellent performance, independent of clinical factors such as Gleason and CAPRA. We believe it will play a significant role in aiding clinicians to select the most appropriate therapy regimen for their patients."

The study was conducted in conjunction with The Movember / Prostate Cancer UK funded Prostate Cancer Centre of Excellence at Queen's University of Belfast and Manchester University along with Cardiff University, University College Dublin, Oslo University and the University of Surrey. Independent assay validation was performed using 322 radical prostatectomy samples with Metastatic Assay positive patients having increased risk of biochemical recurrence (Multivariable HR 1.62; p= 0.0092) and metastatic recurrence (Multivariable HR=3.20; p=0.0001). A combined model with CAPRA-S identified patients at increased risk of biochemical and metastatic recurrence superior to either model alone (HR=2.67; p<0.0001 and HR=7.53; p<0.0001) respectively.

For further information:
T: +44 (0)2838 332200
@AlmacGroup W: almacgroup.com

Unveiled on show floor, Halcyon simplifies and enhances image-guided volumetric IMRT

In front of a large crowd at the annual meeting of the European Society for Radiotherapy & Oncology (ESTRO 36) on May 6th, Varian Medical Systems unveiled the Halcyon™ system, an entirely new device for cancer treatment. The audience at the unveiling were among the first in the world to see this new system which simplifies and enhances virtually every aspect of image-guided volumetric intensity modulated radiotherapy (IMRT).

"The reception Halcyon received at the unveiling, and from attendees coming to the booth has been tremendous," said Kolleen Kennedy, president of Varian's Oncology Systems business. "People have been impressed in the simplicity of the design and how we have automated the system to make it easy for therapists, physicists and physicians to deliver high quality treatments around the world."

"I was pleased to be present at the ESTRO unveiling of Varian's new treatment system," said Professor Gabriela Studer, head of radiotherapy at Kantonsspital in

Lucerne, Switzerland. "There seems to be a great deal of interest in the Halcyon system, which we believe could add to the speed and efficiency of advanced, image-

For more information on Halcyon visit www.varian.com/halcyon
@VarianMedSys

Blue Faery Grants Liver Cancer Research Award to Dr Amit Singal

Primary liver cancer, also known as Hepatocellular Carcinoma (HCC), is the second leading cause of cancer deaths worldwide. Blue Faery created the award to recognize medical professionals who develop innovative research in the fight against HCC, which has no cure.

This year's recipient of the Blue Faery Award (BFA) is Dr Amit Singal who states, "I am truly honoured to receive the Blue Faery Award for Excellence in Liver Cancer Research, and it is a privilege to be among the leaders in the HCC field who previously won the award. I have strived to improve HCC early detection and prognosis through my research, and this award helps reinforce the importance of these goals. I look forward to continue working with your group on improving outcomes for patients at-risk and/or with HCC."

Dr Singal is an expert in Hepatocellular Carcinoma, particularly in early tumour detection and screening process failures. He serves as Clinical Chief of Hepatology and Medical Director of the Liver Tumor Program at UT Southwestern Medical Center. Dr Singal is leading several federal and state-funded projects to evaluate interventions to improve the effectiveness of early tumour detection efforts among patients with cirrhosis. He has published several book chapters on HCC and over 100 peer-reviewed publications.

Dr Singal will receive $3,300 and a custom Blue Faery plaque to commemorate his achievement.

For further information visit: www.bluefaery.org
@BlueFaeryLiver

To have your event listed in the Oncology News diary, E: patricia@oncologynews.biz by June 10th 2017.

2017

May

Annual Trainee Oncology Meeting
13-14 May 2017; Belfast, UK
www.rcr.ac.uk/clinical-oncology/events
E: conf@rcr.ac.uk
T: +44(0)20 7406 5942

Targeted treatments for cancers of the digestive system – How do they work and where are we now?
15 May 2017; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

Association of Breast Surgery Conference
15-16 May 2017; Belfast, UK
T: +44 (0)20 7869 6853
E:jackiespencersmith@absgbi.org.uk

Advances in Nutritional Care of the Cancer Patient
17 May 2017; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

Targeted Treatments for Breast Cancer
25 May 2017; Manchester, UK
E: education.events@christie.nhs.uk
https://ttbreast-cancer.eventbrite.co.uk

June

QI workshop (part 2)
5 June 2017; London, UK
E: conf@rcr.ac.uk
@RCRadiologists

Communications meeting and Sylvia Lawler prize meeting
7 June 2017; London, UK
T: +44 (0)207 290 2982
W: www.rsm.ac.uk/events/OCH04

5th International CNS Germ Cell Tumor Symposium
7-10 June 2017; Columbus, OH, USA
T: +1-614-355-0676 or
E: cmeoffice@nationwidechildrens.org

UK Childhood Cancer Conference
9 June 2017; London, UK
http://www.childhoodcancerconference.org.uk/

NEW
ASCO 2017 National Update, Roy Castle Lung Cancer Foundation, In partnership with BTOG
9 June 2017; London, UK
E: jackie.tebbs@roycastle.org

BAHNON National Conference
9 June 2017; Birmingham, UK
W: http://bahnon.org.uk/

8th International Conference on Children's Bone Health (ICCBH)
10-13 June 2017; Würzburg, Germany
E: iccbh@ectsoc.org
W: www.iccbh.org

Oral Mucositis and Effects of Chemotherapy on Cancer Patients - UKOMiC Study Day
12 June 2017; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

NEW
Myeloma Academy Haematologists' Roadshow
13 June 2017; Bath, UK
E: academy@myeloma.org.uk or
T: +44 (0)131 557 3332
W: www.myeloma-academy.org.uk
Twitter Tag: #MyelomaAcademy

Consequences of colorectal cancer and its treatment
13 June 2017; London, UK
E: clairetaylor8@nhs.net

NEW
Myeloma Academy Nurses' Roadshow
14 June 2017; Bath, UK
E: academy@myeloma.org.uk or
T: +44 (0)131 557 3332
W: www.myeloma-academy.org.uk
Twitter Tag: #MyelomaAcademy

An Introduction to Cancer: Anatomy, Biology and Treatments
14–15 June 2017; Manchester, UK
E: education.events@christie.nhs.uk
https://intro-to-cancer.eventbrite.co.uk

Tumour Microenvironment – Basic Science to Novel Therapies (Including 3D models workshop)
14-16 June 2017; Nottingham, UK
@TheBACR
www.bacr.org.uk

4th Pediatric Neuro-Oncology Basic & Translational Research Conference
15-16 June 2017; New York, USA
www.soc-neuro-onc.org/
pediatric-neurooncology-research-conference/

NEW
NCRI and BTOG Lung CSG Annual Trials Meeting
16 June 2017; London, UK
BTOG
T: + 44 (0)116 250 2811
E: dawn.mckinley@btog.org
W: www.btog.org
Twitter @BTOGORG

Workshop on Methods in Clinical Cancer Research
17-23 June 2017; Zeist, Netherlands
www.ecco-org.eu/Workshop

CO Audit conference and poster competition: The great debate
19 June 2017; London, UK
E: conf@rcr.ac.uk. @RCRadiologists

Introduction to Immunotherapy by Elaine Vickers
20 June 2017; Manchester, UK
E: education.events@christie.nhs.uk
https://intro-immunotherapy.eventbrite.co.uk

Supervisor Skills
20 June 2017; London, UK
E: conf@rcr.ac.uk
@RCRadiologists

Menopause and Cancer Conference
21 June 2017; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

BNOS 2017 Engaging Science Enhancing Survival
21-23 June 2017; Edinburgh, UK
W: www.bnos2017.efconference.co.uk

Nurse - Led Clinics: Preoperative assessment
(2-Day Programme)
22-23 June 2017; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

2nd EACR-AACR-SIC Special Conference
24-27 June 2017; Florence, Italy
www.ecco-org.eu/EAS2017

NEW
7th International Conference on Tumor-Host Interaction and Angiogenesis
25-28 June 2017; Ascona, Switzerland
www.unifr.ch/med/mva2017

3rd EACR Conference on Cancer Genomics
25-28 June 2017; Cambridge, UK
www.eacr.org/conference/cancergenomics2017

NEW
Lymphoma Management
26-27 June 2017; Oxford, UK
E: conferences@lymphomas.org.uk
W:www.lymphomas.org.uk/keble

9th WIN Symposium on Expediting Global Innovation in Precision Cancer Medicine
26-27 June, 2017; Paris, France
E: win@congressbydesign.com
W: www.winsymposium.org

NEW
Cytotoxic Medication Study day for Nurses new to Cytotoxic Treatment
27 June 2017; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays
@trmeducation

ESMO World GI Congress
28 June-1 July 2017; Barcelona, Spain
W: esmo.org

NEW
Haematology: Chronic Lymphocytic Leukaemia
29 June 2017; Manchester, UK
E: education.events@christie.nhs.uk
https://c-l-l.eventbrite.co.uk

Engaging Science Enhancing Survival

Wednesday 21st – Friday 23rd June 2017

Preliminary Programme and Faculty are now available

British Neuro-Oncology Society

Venue: John McIntyre Conference Centre, University of Edinburgh
Dedicated Parallel Quality of Life Sessions for Nursing staff and Allied Healthcare Professionals
Keynote Speakers: James Perry, Toronto – Late Effects and Anthony Byrne, Cardiff – End of Life Care
Welcome Reception: Dynamic Earth
Gala Dinner: Playfair Library, Old College, University of Edinburgh

Visit **www.bnos2017.efconference.co.uk** for further information – *See you there!*

@BNOSofficial

European Head & Neck Course
BIRMINGHAM-AMSTERDAM-POZNAN

10th Annual EUROHNC

Poznań 15th - 17th November 2017
POLAND

Standards, innovations, perspectives and possibilities in head and neck oncology

Course Directors:

- Wojciech Golusiński (Poland)
- René Leemans (The Netherlands)
- Sat Parmar (United Kingdom)
- Paul Pracy (United Kingdom)

More information on the website:
www.eurohnc.com

EHNS

Main topics:

- Multidisciplinary treatment of head and neck
- Neck
- Oral cavity and oropharyngeal tumours
- Larynx and hypopharynx
- Salivary gland tumours
- Recurrent head and neck cancer
- Reconstructive surgery
- HPV in head and neck cancer
- Modern radiotherapy - protons
- Chemiotherapy - new frontiers
- Rehabilitation
- Future perspectives
- Skin cancer
- Case discussion

For all EUROHNC Participants the CME credits will be granted

BTOG – CPD Educational Events 2017/18

NCRI and BTOG Lung CSG Annual Trials Meeting

Friday 16th June 2017

Cavendish Conference Centre, London

Free registration for HCPs. Programme, registration and call for trial proposals – www.btog.org

---

ASCO 2017 National Update
Roy Castle Lung Cancer Foundation In partnership with BTOG

Friday 9th June 2017

Wellcome Collection, 183 Euston Road, London – 13:30 to 15:30

Places will be allocated on a first come first served basis. Free registration for HCPS. Please register your attendance with jackie.tebbs@roycastle.org

---

BTOG - Immunotherapy 2017 – The Essential Update

Friday 24th November 2017 – please save the date

Wellcome Collection, London

Free registration for HCPS. Further information available soon

---

BTOG 2018 – 16th Annual BTOG Conference 2018

Wednesday 24th to Friday 26th January 2018 – please save the dates

Dublin

Poster submission opens 1st August 2017 and closes 1st October 2017

Registration and hotel booking opens 1st September 2017

The Vision of BTOG is to ensure equitable access to optimal care for patients with all thoracic malignancies in the UK and Ireland. The Missionof BTOG is to support and educate health care professionals, creating a professional community to exchange ideas, information and innovation and to foster the development of research. The overall aim is to represent the needs of patients and improve their outcomes. The Steering Committee Chair of BTOG is Dr Sanjay Popat.

Secretariat: British Thoracic Oncology Group (BTOG) – Charity No. 1166012
Glenfield Hospital, Leicester LE3 9QP
Email: dawn.mckinley@uhl-tr.nhs.uk
Telephone: 0116 250 2811

Website: www.btog.org **@BTOGORG**