prof.dr. James Hardwick

Colon cancer through the looking glass

Universiteit Leiden

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Colon cancer through the looking glass

Inaugural lecture by

prof.dr. James Hardwick

on the acceptance of his position as professor of

Gastroenterology and Hepathology,

in particular the Early Detection and Treatment of Colorectal Tumours

at the Universiteit Leiden

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Leiden

’Twas brillig, and the slithy toves
Did gyre and gimble in the wabe:
All mimsy were the borogoves,
And the mome raths outgrabe.

“Beware the Jabberwock, my son!
The jaws that bite, the claws that catch!
Beware the Jubjub bird, and shun
The frumious Bandersnatch!”

He took his vorpal sword in hand;
Long time the manxome foe he sought—
So rested he by the Tumtum tree
And stood awhile in thought.

And, as in uffish thought he stood,
The Jabberwock, with eyes of flame,
Came whiffling through the tulgey wood,
And burbled as it came!

One, two! One, two! And through and through
The vorpal blade went snicker-snack!
He left it dead, and with its head
He went galumphing back.

“And hast thou slain the Jabberwock?
Come to my arms, my beamish boy!
O frabjous day! Callooh! Callay!”
He chortled in his joy.

’Twas brillig, and the slithy toves
Did gyre and gimble in the wabe:
All mimsy were the borogoves,
And the mome raths outgrabe.

Mijnheer de Rector Magnificus, zeer gewaardeerde toehoorders, honoured guests, ladies and gentlemen,

some of you may now be wondering whether you haven't taken a wrong turn and ended up in a poetry seminar, others of you will be wondering, much like Alice in Lewis Carrol's 'Through the looking glass' when she found and read this poem, "What is this nonsense?"

Monster

Jabberwocky is one of the most famous nonsense poems in the English language and forms part of the fantastical world that Alice, following on from her adventures in wonderland, finds on stepping through a looking glass. Upon finding the poem, Alice realises that she needs the looking glass (here a mirror) to read it at all as it is written in mirror-writing, and even then it appears to be largely nonsense. Later in the book she meets Humpty Dumpty who tries to explain the poem to her. So sitting up on my wall here and without falling off I will try to explain things to you, while taking you on a short trip through the looking glass into the world of colon cancer.

The poem is clearly about a fearsome monster, finding it and ultimately decapitating it. Cancer is indeed a monstrous disease and the disease that everyone fears. Hippocrates seems to have started the monster metaphor referring to the disease as 'karkinos', Greek for crab, perhaps referring to the hard round shell and sharp claw like projections. In Greek mythology Karkinos, a monstrous giant crab, was sent by Hera to distract Heracles from killing the Hydra. One swift kick from Heracles cracked the shell and killed Karkinos. The Roman physician Celcus then translated the Greek Karkinos to the Latin 'Cancer'. So Cancer is a monster that grabs you in its claws while you least expect it. Colon cancer is particularly scary in this respect because it creeps up so unexpectedly, growing unseen, without symptoms, without obvious risk factors and it is frequently fatal. Cancer is not only monstrous for the individual but after a century in which we conquered infectious disease followed by an era where health was dominated by heart disease we are now moving into a new era where cancer will be the worlds greatest threat to health.[1] Among the various different types of cancer, colon cancer is the second biggest killer after lung cancer, with 1 in 20 of us developing the disease within our lifetime.

Cancer metaphors

Metaphors have a long tradition in cancer. In 1971 President Nixon famously declared war on cancer, thereby unwittingly setting a dangerous precedent for US presidents to declare war on nebulous adversaries! No other disease attracts the use of violent military metaphors in the way that cancer does. Cancer is described as an "evil, invincible predator" with "cells that invade the body". Patients are "bombarded" with radiation, and receive chemotherapy that is portrayed as "chemical warfare that destroys to save". The discussion about the impact of these metaphors is still lively with breast cancer sufferer Susan Sontag arguing that their use shames patients who are not only ill but then implicitly 'lose' or 'give up' if the disease progresses. However, metaphors are a colourful way to conceptualise disease so I intend to continue in this tradition. How can we find and defeat this Jabberwock that is colon cancer? Accepted wisdom would suggest that you should know your enemy, requiring a fair amount of 'uffish' thought. You've also got to find the 'manxome' foe in the 'tulgy' wood. You've got to be able to recognise the enemy; are you sure it's the Jabberwock you're looking for and not the Jubjub bird or the Bandersnatch? And if other subtler approaches fail you can always take your vorpal sword and lop off its head!

Understanding the enemy

There are various levels at which you can try and understand colon cancer in order to prevent and treat it and both in my clinical practice and my research I have been active in several of these areas. Understanding begins with observation and in cancer this began with the naked eye.

Looking glass I

However, early observation of cancer with the naked eye even after dissection of the human body became acceptable, failed to increase understanding appreciably. Cancer remained a disease caused by Gods or bodily humors from the time of the Ancient Egyptians right up the 19th century. More successful attempts at deciphering the cancer riddle required a looking glass, not a mirror as in Alice's case to decipher Jabberwocky, but the microscope. The microscope enabled the German pathologist Johannes Muller to develop his Blastema theory, that cancer was made up of cells and not caused by lymph or humors. Even today when the last 2 decades have seen more advancement in the understanding of cancer than the rest of history put together, observations through a simple light microscope continue to be the mainstay of diagnosis and are often the starting point for revolutionary new theories in cancer biology. A recent example of this is the realisation of the importance of the non-cancerous stroma support cells in colon cancer. Estimation of the degree of stromal reaction at the site of invasion of colon cancers by simple microscopic observation has revealed that cancers with more stromal reaction have a worse prognosis.[2] Subsequently reanalysis of global gene expression studies in colon cancer have shown that the signatures defining a particularly aggressive colon cancer subtype all arise from the non-cancerous support cells.[3] This together with mouse models where manipulations of the support cells both initiate and potentiate cancer growth, have lead to a resurgence of interest in the cancer microenvironment.

Looking glass 2.0

So advances in molecular biology have also enabled us to look at cancer in new ways, moving on from physical to molecular methods. While the microscope revealed the chaotic nonsense that is cancer as being a cellular phenomenon, analysis of DNA revealed it as a genetic disease, and analysis of genes and their function revealed it to be a disease of faulty molecular signalling with gradual corruption of the normal checks and balances controlling individual cell behaviour in a multicellular organ such as the bowel. So our understanding of cancer has been driven in part by the development of new tools with which to look at it: In essence, new looking glasses. Unfortunately, as Alice found, being able to read the poem is only the first step in understanding it. As cancer progresses, its growth becomes increasingly chaotic going into and through adjacent tissues and organs and eventually spreading to distant parts of the body as metastases. In the same way the cancer genome, its DNA, becomes increasingly chaotic as layer upon layer of ingenious mechanisms to detect and repair DNA damage are corrupted. As we develop new ways of looking at cancer in a global unbiased fashion and delve deeper by developing new ever more complex technologies, each time we are faced with the problem of how to interpret what we find. The so-called 'omics' technologies such as genomics, transcriptomics and proteomics have captured the public imagination. The hope is that this sort of 'Big Science' will combine the mysterious magic of 'big data' with massive computer power and somehow, almost without the need for a question, will reveal answers that careful hypothesis driven, small scale research have failed to reveal. I think this optimism, certainly in colon cancer, is unfounded. We may be able to accurately say which of the 25,000 genes is mutated and at what frequency; which genes are silenced through methylation and to what degree; which genes are deleted or amplified, which genes are expressed at RNA level and which proteins, short hairpin RNAs and other non-coding RNAs result. But can we then calculate the integrated effect of these changes on the various cellular signalling pathways that control cell function? Trying to decipher the chaos remains a gargantuan task. You could liken it to working out the root cause of an air crash while only having access the resulting wreckage. Just because the wing of the plane is broken off in the wreckage does not mean this was the cause of the crash. Colon cancer, through this sort of looking glass is for a large part rubbish arising from collateral damage whose decryption is as subjective as interpreting Jabberwocky.

Inherited cancer syndromes

Luckily there are lines of evidence for molecular research into colon cancer that provide simpler more focussed starting points, a bit like finding the black box flight recorder after the air crash. Colon cancer has a strong hereditary element. As far back as 1895 families have been identified where multiple family members develop colon cancer. Subsequently the underlying genetic mutations and molecular pathways have been identified. Inherited cancer syndromes are caused by inherited mutations. Families with the syndrome include those with the disease and those without. By comparing the DNA of those with to those without, the segment of DNA responsible can relatively easily be found and genes within these segments checked for mutations. In this way cancers arising in a family can be seen to be due to a mutation in one gene, the air crash can be attributed to one faulty warning light. However, inherited colon cancer is only responsible for a tiny proportion of all colon cancers. The importance of these rare cancers is that they allow us to identify genes in which mutations are the root cause of colon cancer and not just the result of the massive collateral damage caused during disease progression. When we take this knowledge back to the non-inherited majority of colon cancers, we often find the same genes are mutated or other genes within the same signalling pathway, leading to the same net result. It is one of these pathways, identified initially in families suffering from Juvenile Polyposis syndrome, which I have been specifically investigating now for 15 years.[4] The Bone Morphogenetic Protein, or BMP pathway, gets its name from where it was initially discovered, in bone. But it does much more than influence bone growth leading some to suggest it be rechristened the Body Morphogenetic Protein pathway. Now on the surface it may seem that studying one signalling pathway in one disease must be pretty limited, ridiculously specialised. But the fascination of cancer biology is the insights that disease gives into the intricate workings of the building blocks of life itself. While early anatomists like Boerhaave wondered at the grotesque foetal malformations leading to children with one central eye like the Cyclops, too many fingers or fused legs like a mermaid, we now see with the same fascination similar monstrous deformities in a microcosm. We see how cellular organisation of the microscopic fingers or villi of the intestine can be corrupted by alterations in the signals cells use to orientate themselves in 3 dimensions, so-called morphogens like BMP. Often it is even the same signals that perform similar organisational functions in both the embryo and the intestinal villi. So while Hedgehog pathway disruption leads to one-eyed Cyclops babies, it also leads to mutant intestinal villi. Likewise changes in levels of BMPs lead to children born with too many fingers and, in the microcosm of the intestinal villus, to cells mistakenly thinking that they are at the bottom of the villus when they are actually in the middle, and then starting to make new mutant fingers half way up and at right angles to an existing finger. In this way we can begin to explain the weird patterns of growth that the pathologists observe in colon polyps down the microscope and use to classify them. So together with many other research groups worldwide I have been involved in trying to establish exactly how the inherited changes leading to colon cancer do their damage.[5] It's the same sort of fascination that makes air crash investigations popular television viewing. Can we trace and explain all of the steps leading back from the disaster to the one faulty screw?

Fundamental research under pressure

The paradox with fundamental molecular research is that, despite the fact that all the new cancer therapies stem from better molecular understanding of cancer, there is a growing disillusionment with it and especially the time frame from new molecular understanding to translation into a new cure. It is increasingly difficult to secure funding for molecular research with funding bodies putting more emphasis on research where the implications for patients are more immediately apparent, perhaps influenced by the trend to involve patient groups in funding decisions. As cancer research continues to split into an ever expanding number of disciplines from psychological impact, to nutrition, advances in surgery,

endoscopy, imaging, quality of life, pharmacology, patient value and systems biology, competition for limited research resources is increasingly determined by short term societal impact. To my mind we have embarked on an irrevocable course; the desire to understand the human body and disease at the most fundamental level possible and if initial optimism as to the time this would take was unfounded, we should only redouble our efforts. We need more clinician scientists involved in basic research and careful nurturing of this career path. When I started my PhD it was clear to me that clinicians of the future should be schooled in basic science and that real research involved active participation in the molecular revolution. I'm not sure that this view is still dominant among physicians in training today. We have to be wary of a dumbing down of medicine with original thinking making way for slavish guideline following and where basic research is left to biologists.

To return to our military campaign against the Jabberwock; while attempts to understand the monster at a nuts and bolts level, at the level of DNA and molecular pathways, are leading to an increasing armoury with which to battle advanced colon cancer, the number of patients ultimately dying from the disease has not changed dramatically. How else can we approach it?

Prevention

One attractive way is to try and prevent the disease in the first place. How and where do Jabberwocks breed and can we destroy their breeding grounds? Risk factors for colon cancer have been identified from large epidemiological studies. Smoking, obesity, and a Western lifestyle are the most important modifiable risk factors in which diet and limited physical activity are the most important aspects of the Western lifestyle that lead to an increased risk. Vast amounts of research have been performed to try and identify the specific dangerous components of the Western diet. Red meat, burnt red meat, processed meats, saturated fats, cholesterol and fibre have all been implicated but perhaps the strongest evidence is for a general role for energy imbalance, too many calories being consumed and too few expended. I have been involved with trying to identify the molecular mechanisms for some of these risk factors. One interesting observation has been that the obesity hormone Leptin can stimulate colon cancer cell growth and thus is likely to be one of the factors coupling obesity with a higher risk of colon cancer.[6]

A further long recognised factor protecting against colon cancer is the regular use of certain drugs, particularly Aspirin and cholesterol lowering drugs. These observations have spawned a whole new field aiming to prevent colon cancer with drugs, so called chemoprevention. What the field makes painfully clear is that one of the big challenges is performing the extremely large and long running trials needed to prove the effectiveness of this approach. This is especially true for older cheaper drugs such as Aspirin where there is little incentive for big pharmaceutical companies to fund such trials. In fact there are good reasons why they should be extremely circumspect with regard to such trials. In 2004 Merck had to withdraw the anti-inflammatory drug Vioxx from the market after results from a large chemoprevention study in colon cancer clearly confirmed an increased risk of strokes and heart attacks.[7] Vioxx had generated 2.5 billion dollars in sales revenue in the previous year and had been used by 80 million patients worldwide. Trying to expand the indications for the drug to include the chemoprevention of colon cancer, which would have likely been a minor indication compared to its use as a painkiller, proved fatal. Subsequently it has become clear that many similar painkillers, for example Ibuprofen, have a similar risk profile, also increasing the chance of stokes and heart attacks. However, the drug remains withdrawn and Merck has had to pay more than 5 billion dollars in court settlements. The dramatic negative consequences of performing the extremely expensive, large, long-term trials needed to establish a drug as a chemopreventive agent with the uncertainty that they will be widely used for this purpose has major implications for

this field. My particular area of interest in chemoprevention has been the cholesterol lowering drugs, the statins. This was sparked by the results of a large pharmacological screen for drugs that influenced the Bone Morphogenetic Protein pathway. This screen showed that of the 30,000 drugs tested, the 2 most effective in stimulating the BMP pathway were 2 Statins. Subsequently we have gone on to show that Statins can kill colon cancer cells by stimulating the BMP pathway.[8] Our most recent research, together with the department of surgery in the LUMC, has shown that continuing to use Statins after an operation for colon cancer strongly reduces the chance of dying overall.

Holistic prevention

Interestingly one of the criticisms of this study was; could we be sure that the statins weren't just reducing the chances of dying from heart disease? The implication being that if that was the case then the result was irrelevant. Well from other similar studies we know that about 85% of the deaths in patients operated on for colon cancer are due to the cancer itself. However, it does reveal a very blinkered, monomaniacal approach to disease that is very prevalent. Colon cancer researchers are only interested in deaths from colon cancer and strategies to prevent or intervene in colon cancer rarely take other concurrent diseases into consideration. However for the patient a more holistic approach makes much more sense. How you die is of less importance than whether you are alive or dead. Colon cancer shares many of the same risk factors as cardiovascular disease and for this reason many patients suffer from both at the same time.[9] Currently health care focuses on one or the other of these problems entirely separately. So major investments are made in one area, a bypass or coronary stent, without a simple screen for colon cancer and likewise colon cancer screening programs pay no attention to concomitant cardiovascular disease. A more holistic approach specifically in this area would perhaps address the anomaly that despite the fact that we know screening for colon cancer is effective at reducing deaths from colon cancer, they currently have no effect on mortality overall.[10] The implication is that we can save patients from their colon cancer but they nevertheless die at approximately the same time from a stroke or a heart attack.

I think that this can potentially be improved by combining screening for colon cancer with screening for cardiovascular disease. This may mean that the choice as to which screening technique to use in the future should take into account the possibility of integrating it with cardiovascular screening. For instance testing for both from the same blood sample or simultaneous colon and coronary artery CT scanning. I also think treatment would benefit from more emphasis on mortality overall. Our studies would suggest that a simple low risk combination of Aspirin and a statin especially in the ever larger group of colon cancer patients of advanced age, poor health from other diseases or with a low a risk of the cancer recurring, could improve overall mortality. However, this unglamorous approach still requires large randomised controlled trials to prove it beyond doubt and it is questionable whether such trials will attract sufficient funding to be able to perform them.

So far I have covered relatively subtle ploys to address the threat of colon cancer but as we have heard in the poem, the traditional and still most common approach to the Jabberwock is distinctly less subtle and in essence boils down to variations on the theme of 'taking your vorpal sword in hand'. However, before the exciting and fulfilling 'snicker-snack' and proudly galumphing back with its head the gastroenterologist hero of this story has to find the enemy. As endoscopists we're most keen to find fledgling Jabberwocks before they become fully grown monsters; colon polyps.

Finding the enemy: looking glass III

To do this we make use of a particular type of looking glass, a flexible endoscope. When I began in endoscopy there was little or no consideration given to finding colon cancer or polyps. We were content to have reached the end of the colon at all

and cancers or polyps were either obvious in which case they jumped out and hit you in the face, or they were not there. The alternative, a barium enema was even worse so we could perhaps be forgiven for our complacency. It was the Japanese who first raised awareness of the existence of what we now call non-polypoid polyps, a wonderful Oxymoron that could be straight out of a nonsense poem. So suddenly some polyps weren't polyps at all. Worse was to follow as after thinking that we could tell the harmless polyps from the dangerous ones, it suddenly transpired that we'd got it the wrong way round. Polyps previously classified as hyperplastic and therefore irrelevant and innocuous, requiring no treatment and no follow up, were suddenly reclassified as sessile serrated polyps. Worse still, they were frequently flat, often not recognised at colonoscopy and were probably more aggressive than classic adenomatous polypoid polyps.[11] Now we not only had to find the Jabberwock but also the Jubjub bird and the Bandersnatch. Suddenly colonoscopy couldn't be trusted any more. Frightening figures for the percentage of polyps missed at colonoscopy[12] and the chance of developing cancer after a colonoscopy[13] confirmed that finding and recognising cancer precursors by looking with normal white light was far less accurate than we had thought. Ironically increased awareness of the fallibility and potential inaccuracy of colonoscopy occurred at the same time as dramatic improvements in both equipment and its technical performance. As any of you who have made videos with successive generations of smartphones will appreciate, the latest generation colonoscopes have incomparably better resolution than their predecessors. Training in colonoscopy has also improved dramatically including, for example, more use of simulators, a bit like training pilots with flight simulators. The problem is that recognition of polyps at standard colonoscopy still relies on them protruding from the colon wall and having a different colour than the surrounding normal colon; in other words their physical characteristics. Flat polyps show neither of these discriminating attributes. One solution has been to spray a blue dye onto the colon wall and indeed a large Dutch trial of this technique in patients with inherited colon cancer is nearly complete. This should make it clear whether it has added value compared to standard white light endoscopy. It is not the most user friendly of techniques requiring quite laborious spraying of the dye onto all areas of the colon wall. This topical application of dye to the colon is fraught with difficulty. Deep folds and sharply angulated segments of the colon, residual faeces and adherent mucus all severely hinder advanced imaging techniques that rely on topical application of a dye. A simpler technique uses blue light instead of white to help detect polyps. This can be performed at the touch of a button but blue light mainly helps in the classification of polyps close up. Could fluorescent light help to identify polyps? Initial work in this area made use of autofluorescence and at wavelengths at which faeces also fluoresces. Autofluorescence, or the natural fluorescence of the colon, can be assessed with the touch of a button on the endoscope but in trials in clinical practice it has proved of little added value in finding polyps.

Looking glass 4

Perhaps what is needed is a fundamentally new type of looking glass for use in the colon, again moving on from physical to molecular. Wouldn't it be nice if we could tag polyps with a fluorescent marker at a wavelength where there is no background in the colon so that polyps would fluoresce and shine out clearly like light bulbs from the normal colon? And, of course, we don't want any of that messy dye spraying so it has to be given intravenously and, of course, it has to be completely safe. Sounds like science fiction! But recently we have published our first experiences with a prototype near-infrared colonoscope and an intravenously delivered fluorescent-labelled probe that specifically sticks to polyps. With this system polyps glow bright green in the dark allowing us to detect a number of flat polyps that were invisible with normal white light colonoscopy.[14] We've given the Jabberwock eyes of flame! This raises the exciting prospect of molecular imaging opening the way for much more accurate detection of not only cancer but also, for example, nerves. This will allow

surgeons and endoscopists to see things in real time that we cannot see with normal light.[15]

Vorpal sword

So now after a long search in the 'tulgy' wood we've found the 'manxome' foe. The real thrill of endoscopy came with the development of weaponry to attack the monster. This began simply. The classical Jabberwock polyp with a bulbous head and a long neck is relatively easy prey. It is quite simple to pass a wire loop over the head of the polyp and 'snicker-snack', or in this case a few beeps from the electrosurgical unit, and you're galumphing back with its head. Things become trickier when the polyp has no neck and is too big to fit into the wire snare in one piece. Large numbers of this sort of polyp are still referred to the surgeons for removal of a segment of colon containing the polyp but increasingly they can also be removed endoscopically. We are approaching the point where it is technically possible to remove all polyps endoscopically wherever they are in the colon. Endoscopic removal can usually be done on an outpatient basis and complications especially when compared to the short and long term complications of the alternative surgical treatment, are infrequent and minor.[16] Endoscopic therapy is the ultimate in minimally invasive, organ sparing surgery avoiding the chances of thromboembolism, wound infection, faecal incontinence, impotence, chronic abdominal pain, hernias and adhesions that are all part of the package of classical open surgery.

Risk in endoscopy

So why do large numbers of patients continue to be treated surgically for benign polyps? The reasons for this are threefold. Firstly, perverse financial incentives. There are large financial disincentives to performing extensive endoscopic resections. Removing any polyp, whether 1 millimetre or 10 centimetres in diameter attracts the same fee while removing large polyps is many times more expensive, making it a loss making activity. Surgery for the same polyp attracts a much higher fee and is thus a much more profitable option for hospitals. Healthcare costs are driven up and patients suffer, but insurers and patients are not aware of this. Patients are usually very relieved to hear afterwards that the unnecessary operation was successful and that it wasn't cancer after all but a benign polyp. Secondly, logistical pressure on endoscopy capacity. Carefully removing a big polyp can take several times as long as a normal procedure. Its not easy to accurately estimate how long such a procedure will take and thus difficult to plan efficiently. The waiting lists and the sheer volume of colonoscopies arising from screening and a relative shortage of colonoscopists make it attractive to refer big polyps to the surgeon.

Thirdly, insufficient awareness and lack of data on relative risks. As physicians, colonoscopists are relatively risk averse. Colonoscopy was initially developed as a purely diagnostic tool. Therapy for bowel cancer and its precursors remained in the hands of the surgeons. However, increasingly the two once separate fields have come to overlap with endoscopic or surgical alternative approaches to the same problem. Colonoscopists have had to slowly acclimatise to the new potential for intervention and along with this acceptance of the accompanying risk of complications. This sometimes leads to risk avoidance strategies that ironically put the patient at more risk. Endoscopic removal of a large polyp is a high-risk endoscopic procedure. Undertaking it will likely lead to a higher complication rate for the performing endoscopist and questions from colleagues and review boards. For many endoscopists fear of complications leads them to refer the patient for surgery and segmental bowel resection. On the surgical side of the fence the same problem looks entirely different. Compared to removing an advanced cancer it is a relatively simple procedure with a low complication rate. Any eventual complications will not be collected in a National Registry, as there is only a registry for operations for cancer. But these low surgical risks are still probably ten times higher than those of the 'too risky' endoscopic procedure. Unfortunately data collection is at present too poorly performed to allow accurate calculation and comparison of these two risks. So while we can be proud to have initiated

colon cancer screening programs throughout much of Europe, there is still scope for fine-tuning the treatment especially of large polyps.
This sharp division between surgical and endoscopic worlds, where you almost seem to have to step out of one to step into the other, may also be stifling advances in endoscopy. Endoscopic Submucosal Dissection, or ESD, is a relatively novel advanced endoscopic technique. Here polyps are removed meticulously in one piece and as comprehensively as possible without disturbing the muscle layer of the bowel. In Japan and other far eastern countries it has been embraced as being the ultimate in minimally invasive, organ sparing surgery offering improved pathological staging accuracy, reducing the need for secondary surgical resection and thus potentially reducing morbidity and mortality. From a surgical perspective ESD can be seen as cheap and safe surgery, and this seems to be how it is viewed in the Far East. But from an endoscopic perspective it is a complex, expensive and dangerous alternative to the simpler but messier Endoscopic Mucosal Resection, where the polyp is hacked away in chunks, and this seems to be how it is viewed in Europe. The two worlds of surgery and endoscopy should ideally blend into one with a smooth transition in procedural risk rather than the current stepwise disconnect.

So I hope we will gradually see endoscopic procedures to remove large polyps being treated more like surgical procedures. Concentration in expert centres will be formalised. Complications of both surgical and endoscopic resection of benign polyps will both be registered nationally. This together with individualised computer modelling of the risk of complications will allow direct comparison between surgical and endoscopic treatment options. Reimbursement will be independent of the technique used so that surgical or endoscopic removal of large polyps attracts the same fee and Gastroenterologists will feel equally personally responsible for the surgical risks they expose their patients to, as the endoscopic risks.

Unfortunately as endoscopists we frequently stumble upon monsters where our current endoscopic arsenal has nothing to offer. The standard approach for invasive cancer, even when relatively small, is surgical resection. Nevertheless the last years have seen radical changes in approach specifically for rectal cancer. Strangely this has been simultaneously in two opposite directions. On the one hand surgery has progressed towards removal of increasing amounts of tissue leading to improved survival at the cost of increased morbidity, and on the other the rise of organ sparing minimally invasive approaches such as local radiotherapy. Increasing numbers of elderly patients with rectal cancer, suffering with other chronic diseases at the same time, form an ever-larger group in whom more extensive surgery will be unlikely to increase life expectancy and will be associated with an unacceptably high risk of complications. I believe that endoscopy will have an increasing role to play in minimally invasive cancer therapy as part of a combined approach, and advanced endoscopic imaging techniques will be increasingly employed for the assessment of response and follow up.

So endoscopy in colon cancer has a bright future with the prospect of an ever-expanding role in prevention and treatment with exciting developments in molecular imaging, tissue transplantation, and resection techniques.

And hast thou slain the Jabberwock? Well sadly not yet once and for all. Colon cancer remains a fearsome foe. But we are making inroads, with increasingly successful skirmishes aided by a succession of new looking glasses and at the current rate of progress it is not unthinkable that we will, one frabjous day, celebrate the taming if not the ultimate slaying of the monster.

Word of thanks
At the end of my inaugural lecture I would like to thank those who have contributed towards this appointment, the College van Bestuur of the University of Leiden and the Raad van Bestuur of the Leiden University Medical Center.

Fellow professors, it is a great honour to be accepted into your midst. I would particularly like to thank Ton Rabelink and Peter ten Dijke for their support in my appointment as professor and Gijs van den Brink and Ivo van Schaik for their encouragement and inspiration over the years.

I would like to thank my direct colleagues within the Department of Gastroenterology for their support and friendship over the last eight years in Leiden and colleagues in the endoscopy department, the outpatient department, the inpatient wards and the lab.

Special thanks to Sander van Deventer and Maikel Peppelenbosch for their initial offer of a one year research post in Holland which has now, in a serious case of mission creep, ended with me standing here before you now and still in Holland 15 years later.

Thank you to my friends, mother and father, brothers and sister who have come all the way over from England to be here today and I'm particularly happy that my father can share in this occasion with me.

Tamara, Natasha, Jasper and Boris, it's wonderful to have you all here in the front row supporting your father in silence for an hour. You've behaved yourselves far better than I have supporting you, shouting from the sidelines in your various team sports.

Finally, my wife Eva. You provide the emotional intelligence in our marriage and without your love, understanding and support our family wouldn't function as the warm close unit it is. Thank you fate, and Médecins sans Frontières, for bringing us together and thus leading me here to Leiden, a traditional haven for lost or outcast English, where I feel very privileged to be made welcome.

Ik heb gezegd.

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Wij bevinden ons aan het begin van een nieuw medisch tijdperk waar kanker doodsoorzaak nummer één wordt. De strijd tegen kanker wordt gevoerd met een snel uitbreidend arsenaal van middelen, maar vooruitgang staat of valt met het beter begrijpen van de ziekte. Ons begrip wordt gedreven door het ontwikkelen van nieuwe manieren om naar de ziekte te kijken; nieuwe ‘looking glasses’ zoals DNA sequencing technologie. Maar darmkanker leidt tot zulke chaotische veranderingen op moleculair niveau dat eenvoudige invalshoeken, zoals het bestuderen van erfelijke vormen van kanker, vaak meer bruikbare informatie leveren. Met vooruitgang in moleculair darmkankeronderzoek dreigt de kloof tussen de artsen en de onderzoekers zo groot te worden dat ze elkaar niet meer kunnen begrijpen. In het aanbrekende moleculaire tijdperk zullen clinici met moleculaire kennis steeds belangrijker zijn om deze kloof te overbruggen. De hoop blijft dat er, met meer kennis door ontwikkelingen van nieuwe moleculaire en endoscopische ‘looking glasses’, een tijd aanbreekt waar het monster darmkanker getemd zal worden.

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