

# Balancing cure and care

One surgeon's multidisciplinary quest to raise standards across the board

→ Janet Fricker

**Cornelis van de Velde** went into cancer because he loved the complexity. Throughout his career he has grasped each new development across the disciplines to see how it could help resolve the difficult balance between curing a patient and preserving their quality of life. Spreading excellence in surgery, he says, is the single most important thing Europe can do to improve outcomes.

**W**hen Cornelis van de Velde's youthful ambition of becoming a fighter pilot was thwarted by a Dutch air force's freeze on recruitment, he was forced to turn to his second career choice – medicine. From the outset there was no question he would do anything other than surgery – it required the same macho 'action hero' outlook on life, love of gadgets and gizmos, and hand-eye coordination skills as flying.

Throughout his career as a surgical oncologist, flying has been a recurring theme, helping him transfer the disciplines of quality assurance to the operating theatre. "If your Captain tells you that your flight to Heathrow had a 10% chance of crashing into the North Sea, you don't accept that level of risk. Yet in cancer surgery, every day patients accept much higher levels of risk without question," says van de Velde, who has dedicated his career to minimising those risks and raising standards of care particularly in breast, gastric and colorectal cancer.

"By conducting well-controlled clinical trials in surgery we have been able to make simple improvements that dramatically change outcomes and make a real difference to patients' quality of life," he says.

It has often been an uphill battle, however, as surgeons – surgical oncologists in particular – have been slow to accept the feasibility of conducting clinical trials in their specialty. "There was a real feeling that you could not compare different surgical procedures, since surgery was more of an art than a science, and impossible to control... But we have found that by introducing a rigid system of checklists it is possible to control for the individual skills of different surgeons and introduce proper clinical trials," he says, adding that widespread introduction of good evidence-based surgical techniques has greater potential to improve cancer care across Europe than any new pharmaceutical agent.

Van de Velde appreciates the historical irony that it was a French surgeon barber, Ambroise Paré (1510–1590), who performed the first clinical trials in medicine. Cauterising the wounds of amputees at the siege of Villaine, in 1537, Paré 'randomised' patients between tar and an ointment combined with ligatures – the latter proving to be better for both survival rate and comfort. It's an example van de Velde, who was appointed professor of surgery at Leiden (Netherlands) in 1987, and has headed the



KATHALIJN VAN DE VELDE

Department of Surgical Oncology at Leiden University Medical Center since 1999, is proud to follow. Indeed it was van de Velde who developed the protocol for the first clinical trial ever in the Netherlands for breast cancer, as part of his PhD.

Cornelis van de Velde was born in 1951 in Zevenbergen, a rural community in the south of the Netherlands. The family settled in the area at the end of the Second World War, when his father, Jo, moved to a dental practice. The quiet environment particularly suited his mother, Lien, who had been badly injured in the allied bombing, and lost most of her immediate family. “My mother was the sole survivor when her family home was bombed – her parents and brother, after whom I was named, died

just metres from her. The experience was something she never spoke of.”

As a teenager, van de Velde describes himself as a real ‘dare-devil’, not in the least interested in anything academic. “I started flying at 14, and did my first solo flight at 16, and remember literally screaming with delight. Flying gave me such a wonderful sense of freedom and power, and also opportunities for travel. One summer I did a student exchange with the Israeli air force,” he remembers. There was, however, a more artistic side – in his spare time the young Cornelis also enjoyed playing the piano and painting landscapes in the style of the impressionists.

In 1968 he started his medical studies at the University of Leiden, not far from Amsterdam. As a

student he enjoyed rowing, and backpacking around Europe and North and South America, and he met his wife Kathalijn, who was studying law.

A job administering anaesthetics, in his fourth year of studies, exposed him to many different types of surgery, and he picked up on the challenge of cancer. "The complexity of oncology really appealed to me, particularly the balance you need to strike between doing extensive surgery to enhance cure and limiting procedures to offer patients the best quality of life. The different facets of cancer surgery offered access to so many different areas of medicine," he says.

The year he turned 25, Van de Velde married, started his residency and gained his PhD. His thesis in breast cancer, looking at the role of lymph nodes, the extent of their removal and the value of adjuvant chemotherapy, set the tone for a career in which investigating the concept of preoperative chemotherapy, hormone therapy and radiotherapy has been a dominant theme.

### THE FUTURE IS NEOADJUVANT

Last May, he published the 10-year survival results of the EORTC study of preoperative chemotherapy in primary operable breast cancer. The study demonstrated no survival differences (for either overall or disease-free survival) between breast cancer patients who received chemotherapy preoperatively and those receiving it postoperatively. The use of preoperative chemotherapy, however, was accompanied by an increase in the rate of breast conserving surgery.

Chemotherapy and hormone therapy prior to surgery makes 'intuitive sense', he says, as it permits less extensive surgery and helps to prevent tumour spread. "Tumour manipulation can lead to a shower of tumour cells, and animal studies have also shown that, following surgery, metastatic cells divide faster and have a higher labelling index."



**Action hero.** Van de Velde, seen here on a student exchange with the Israeli air force (front row, second from left), is so busy nowadays that he cannot clock up sufficient hours to maintain either his flying licence or his right to perform certain tricky surgical procedures

The general theme is one he has taken beyond breast cancer into gastric and rectal cancer. He hasn't always found it easy to convince his fellow surgeons, however. At times, says van de Velde, he has felt like a 'failed comedian' when he has done the lecture circuits trying unsuccessfully to persuade other clinicians to change their practice. "Breast and gastric cancer surgeons still find it really difficult to delay surgery," he says.

In gastric cancer he was a co-investigator of the MAGIC trial (Medical research council Adjuvant Gastric Infusional Chemotherapy), published in 2006, which showed that chemotherapy prior to surgery improved the resectability of stomach

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## The five-year survival for stage III disease was 13% in the West compared to 44% in Japan

tumours by 10% and improved five-year survival by 13%, making it the new standard of care.

In rectal cancer he showed that, although total mesorectal excision (TME) combined with preoperative radiotherapy resulted in increased local control, there was more long-term bowel dysfunction in irradiated patients. “But I’m increasingly hopeful that the advent of more tailored therapy will soon allow us to select the patients who’ll benefit most from treatment,” he says.

Most recently he has been advocating preoperative chemotherapy and hormone therapy in breast cancer prior to sentinel node biopsy, since it leads to significantly less lymph node dissection and morbidity for patients.

In 1980 van de Velde and his wife spent six months in the US, where he worked at the MD Anderson (Houston, Texas), and the National Cancer Centre (Bethesda, Maryland). This proved a particularly creative period, most notably pursuing his idea for developing the technique of isolated liver perfusion for patients with metastatic colorectal cancer. He got the idea from hearing about isolated limb perfusion in malignant melanoma.

Isolated liver perfusion is a procedure in which a catheter is placed into the artery providing blood to the liver, and a second is placed in the vein taking blood away from the liver, thereby temporarily separating the liver’s blood supply from the blood circulating throughout the rest of the body. The technique allows four times the maximum tolerated dose of chemotherapy to be directed to the liver.

Van de Velde also developed a safety valve, giving labelled erythrocytes with the treatment to spot any leaks. If a problem developed, the chemotherapy

could immediately be flushed from the body.

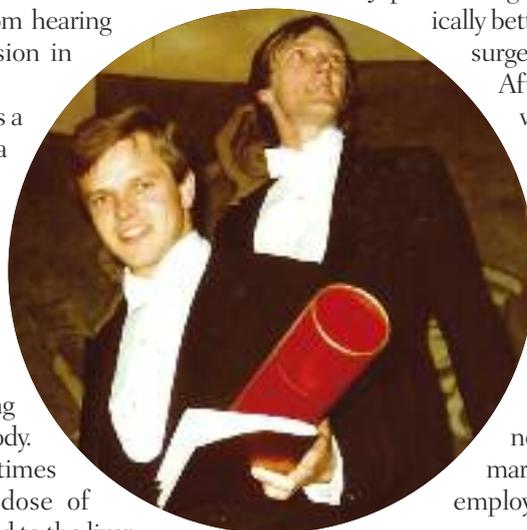
First he performed the procedure on pigs, often sleeping in the lab with his animals, until finally moving on to trials in patients. Results showed that survival could be increased from seven months before isolated perfusion to 24 months for patients exposed to prior chemotherapy and 34 months for chemotherapy naïve patients. But there was disappointment that the technique did not have more potential for cure, as can sometimes be achieved in surgery for liver metastases.

“The logistics of the procedure were extremely complex, since in addition to surgical teams we needed separate teams to monitor for leakage,” says van de Velde, adding that with improved chemotherapy now allowing survival with metastases to 20 months, it is likely that the hey day of isolated liver perfusion has passed.

### A TRIAL OF TECHNIQUES

In the mid-1980s, van de Velde became aware that Japanese surgeons were producing dramatically better outcomes in gastric cancer surgery than surgeons in the West.

After surgery, the five-year survival for stage II disease was 29% in the West, compared to 72% in Japan, and the five-year survival for stage III disease was 13% in the West compared to 44% in Japan. The difference, he found, was that Japanese surgeons undertook more extensive removal of lymph nodes and used wider surgical margins than the standard of care employed in the West. “It seemed



**Who says clinical trials don't work in surgery? Van de Velde, age 25, with his PhD thesis, which included the protocol for the first breast cancer trial ever conducted in the Netherlands**

obvious that we needed to teach our surgeons to operate like the Japanese, but we needed to show that survival differences were due to technique and not some fundamental racial difference in disease," he says.

In 1985 van de Velde visited the National Cancer Centre in Tokyo, working with Keiichi Maruyama, and the Seoul National University Hospital, South Korea, working with Jin Pok Kim, to learn for himself the Japanese way of performing the technique. With a better understanding of the procedure, he initiated a project to bring Japanese surgeons to the Netherlands, to teach Dutch surgeons how to perform the operation. In a randomised controlled trial – where the surgeons were randomised to the different hospitals – they were able to compare outcomes for the Japanese and Dutch approaches to performing the surgery in the same racial population.

But to undertake the trial they first needed to standardise the Dutch approach to surgery. "Studies showed that patients died from recurrent disease when the tumour margins were not big enough, but that more extensive surgery increased the likelihood of their dying from complications," says van de Velde, who over the past 20 years has organised many additional trials to define the optimum extent of surgery.

One notable feature of the Japanese–Dutch randomised trial was that the investigators banked the tissue – a very uncommon practice in those days. This means they are now able to look for candidate markers for selecting patients most likely to benefit from more aggressive surgery.

Despite his wealth of experience, new ideas still have the potential to excite van de Velde. One of his PhD students has just discovered that damage to the levator ani nerve – responsible for motor innervation to the levator ani muscle – explains why faecal incontinence often occurs following surgery for rectal cancer. The nerve was isolated when the researcher correlated common areas of damage in patients who developed incontinence after surgery, and mapped these directly to intact nerves in dissections of cadavers who had died from other causes.

"It's so inspiring that in an old discipline like anatomy we can still be making discoveries in 2008 that have the potential to make a real difference to patients' quality of life," he says.

Van de Velde is also involved with an innovative project using a special camera system that can identify light emitted by injected dyes capable of specifically targeting tumour cells. "This project has two potential applications: it allows the visualisation of tumour margins, thereby promoting more accurate surgery, and it also allows clinicians to see whether sentinel nodes have been invaded by cancer cells without having to open patients up," he says.

### A STRATEGIC SURGEON

Today van de Velde leads a packed life, sitting on numerous national advisory and clinical boards, teaching, lecturing, and pursuing his research activities. He still operates one day a week and sees outpatients on another day, although he no longer takes the lead on more complex surgery. One of the ironies of his quest for improving surgical standards is that he cannot himself always undertake enough annual procedures for quality control purposes. But he is happy to take more of a back seat in surgery, aware that through his international committee work and coordination of trials he can make a more strategic contribution.

He also exerts an influence in supervising PhD students – to date he has supervised more than 50 theses, ranging from surgery to immunology. "My students are the potential surgery leaders of the future, and educating them well is one of the best ways of improving standards," he says, adding that he is achieving an even wider sphere of influence on the next generation through editing the Dutch standard textbook on oncology *Leerboek Oncologie*.

On the national scene, he has been president of the medical section of the Royal Academy of Sciences of the Netherlands, where he chairs a group of 23 medical leaders from the Netherlands who come together to prioritise medical developments and inform the Minister of Health. He has also been

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## “Colorectal cancer survival differs by 10% according to the country in which people are operated”

largely responsible for initiating national groups for breast, gastric and colorectal cancer, that help to translate the results from clinical trials into national standards of care, and has played a key role in the recent creation of the virtual Centre for Molecular Medicine – a joint initiative between academia and industry that allows the sharing of resources such as tumour banks.

In Europe, he is set to become president of the European Society of Surgical Oncology (ESSO) in September, and is in the process of setting up a quality assurance programme for Europe. The scheme, starting first with colorectal cancer, aims to ensure that all patients get access to the best treatments. “In the past protocols have just stated ‘surgery’, without appreciating that surgery is not all the same. For colorectal cancer, for example, there is a 10% difference in survival according to the country in which people are operated,” he says.

At the European CanCer Organisation (ECCO), where he is a board member, he has been promoting interactive workshops, involving international experts. “Oncologists attending these workshops can be really inspired to introduce significant improvements in their day-to-day care of patients,” he says.

Life is undoubtedly hectic. “I don’t have any time for a golf handicap, but I keep fit by walking my Labrador and cycling to work,” says van de Velde, who unwinds at weekends by tinkering with his old Ferrari. Solo flying is no longer feasible, he says with regret, as in recent

years he has not had time to put in the required number of flying hours to guarantee his safety.

Holiday time is particularly precious, though far from relaxing. Van de Velde uses his annual leave to indulge his love of travel and try experiences that are as removed from his daily existence as possible. Last year he was ship’s doctor on a Russian cruise ship to the North Pole, and next January he plans to repeat the experience on a trip to Antarctica. Other recent trips have included skiing in Canada with his wife and their two adult sons, Jan Willem, aged 27, who works with an oil company and Michiel, aged 26, a lawyer, and they have just returned from a trip to Botswana, where they hired a four-wheel drive to view elephants. His flying days may be over, but van de Velde remains above all an action man, both in his professional and personal life.



**Family time.** With holidays like this one, watching elephants in Botswana, it’s little wonder that sons Jan Willem and Michiel opt to come along (the holiday he spent as ship’s doctor on a Russian cruise to the North Pole, however, was just him and wife Kathalijn)