Selecting the Right Drug for the Right Patient - Changing trends in Cancer Management

Dr Lee Soo Chin, Senior Consultant, and Ms Joanne Chio, Head, Clinical Trials, Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS)

The incidence of cancer has been increasing steadily over the years, with lung cancer having the highest incidence rate among men and breast cancer in women globally. The incidence of different cancers varies depending on geographical location, diet, socio-economic and lifestyle behaviors. For example, stomach cancer commonly occurs in Japan, China and Korea, while skin cancer is more common in the United States and Western Europe.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Make</th>
<th>No.</th>
<th>Female</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Colo-rectum</td>
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<td>Breast</td>
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<td>4062</td>
<td>Colo-rectum</td>
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<td>3</td>
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<td>Lung</td>
<td>2057</td>
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<td>4</td>
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<td>1897</td>
<td>Corpus uteri</td>
<td>1574</td>
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<tr>
<td>5</td>
<td>Stomach</td>
<td>1579</td>
<td>Ovary</td>
<td>1455</td>
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Cancer is the leading cause of death in Singapore, making up 29.3 percent of all deaths in 2009. And colorectal cancer is the most frequent cancer in men and breast cancer most frequent in women.

As cancer results in significant morbidity and mortality, and conventional cancer treatment is associated with toxicities, ongoing research is crucial to develop new anti-cancer therapies with better efficacy and lower toxicity as well as to improve and complement existing therapeutics. In the last decade or so, researchers and scientists have capitalised on unique molecular characteristics of cancers to develop targeted and personalised therapy. Personalised therapy focuses on administering the right drug and right dosage to the right patient to optimise efficacy and minimise toxicities; targeted therapy plays an important part in the transition of cancer management to personalised care.

**Targeted therapy**

Decades of scientific and clinical research has resulted in increasing understanding of the biology of cancer. Cancer is a heterogeneous disease arising from genetic changes which lead to the disruption of molecular signaling pathways involved in cellular growth, proliferation and death. Cancers that share similar microscopic features may actually have different genetic makeup, and may be classified into different molecular subtypes that have prognostic and therapeutic implications using advanced diagnostic tools. For example, breast cancers may be divided into luminal, basal-like and HER2 subtypes using molecular profiling which have different prognosis and respond to different treatments. Today, newly diagnosed non-small lung cancers (NSCLC) are routinely tested for the presence of activating EGFR mutations, as 30% of NSCLC in Asia harbor these mutations and demonstrates exquisite response to small molecule EGFR tyrosine kinase inhibitors, such as gefitinib or erlotinib, which are targeted therapy that are much less toxic than conventional chemotherapy.

Such understanding of tumour biology has shifted the paradigm of cancer treatment, and it is now becoming increasingly important to characterise the molecular profile of different cancers with the goal of customising anti-cancer therapy in accordance to its molecular defects.

“Many of the new drugs that block a signaling pathway and cause dramatic responses cease to work after about a year. Lessons learned in treatment of HIV will, in the future, be applied to cancer therapy. One drug against HIV quickly results in viral resistance, but a combination of three drugs works for years because three drugs together prevents resistance. Clearly in the future, we will be using drug combinations to attack multiple pathways simultaneously. Resistance should be prevented and remissions should be long lasting.”

Prof H Philip Koeffler, Deputy Director (Research), NCIS
A biomarker is a biological molecule found in blood, body fluids, or tissues that can be used to measure or indicate the effects or progress of a disease or condition.

Certain unique biomarkers may characterise the molecular defects in cancers and/or serve as therapeutic targets, e.g., activation of tyrosine kinase activity of bcr-abl protein is a hallmark of chronic myeloid leukemia which is in turn, is highly sensitive to imatinib, a small molecule inhibitor that targets the bcr-abl tyrosine kinase. In breast cancer, the expression of estrogen receptor is a marker of response to endocrine therapy, and has been routinely tested for almost two decades to aid oncologists in the selection of endocrine therapy in breast cancer patients. More recently, a rare ALK translocation has been identified in 4% of NSCLC and is associated with dramatic response to an ALK inhibitor, crizotinib, currently in advanced clinical development.

As opposed to the conventional strategy of treating an unselected cancer population, the more focused strategy of matching a tumour molecular defect with a specific targeted agent can improve treatment efficacy as well as shorten the process of drug development.

Targeted therapies are now integral components of treatment for many cancers, including solid tumours such as breast, colorectal and lung cancer, as well as hematologic malignancies such as lymphoma, leukemia, and multiple myeloma. These therapies have improved overall patient survival and prolonged progression-free survival in cancer patients.

“With improved methods to understand tumour genetics and biology, we have come to realise that many biologically different subtypes exist within each tumour types. This also explains why our conventional treatments benefit some but not all patients. In addition, we also better understand the difference between how individuals handle drugs, which explains the different side-effects in patients. This realisation, coupled with new insights into the critical requirement of each of these tumour subtypes, allows us to develop new treatment that will benefit each tumour subtypes with their unique biology. At the same time we can develop tests to help us account for the inter-patient variability and dose drugs appropriately. This type of cancer treatment will become more prevalent in the future as we try to achieve personalised molecularly based therapy.”

Dr Chng Wee Joo,
Senior Consultant,
Department of Haematology-Oncology, NCIS

“Targeted therapy in childhood cancer has benefitted tremendously from the progress made in adults. Targeted drugs like imatinib have transformed the treatment of chronic myeloid leukemia in adults and now in children.”

Dr Allen Yeoh,
Senior Consultant,
Department of Paediatrics,
University Children’s Medical Institute (UCMI), NUH
Mdm E was diagnosed to have breast cancer (HER2+) when she was 32 years old. She underwent surgery followed by conventional chemotherapy.

“Towards the end of my chemotherapy, my doctor informed me of a clinical trial using a new drug Herceptin, targeting HER2+ patient. The trial was a randomized controlled trial. At first, I did not want to enter the trial, but decided to do so after strong encouragement from my mother. My doctor strongly supported me too. Eventually, I received Herceptin for two years. It has been eight years since my diagnosis and chemotherapy treatment. I am more relaxed now and I truly want to see my kids grow up. Entering the clinical trial may have helped save my life. I am confident in the modern treatment that is available now for breast cancer”.

“I am a cancer patient with a specific molecular cell type...
Clinical trials play an integral part in cancer drug development and allow the validation of efficacy and evaluation of safety of new agents. In clinical trials, the effectiveness of new therapies and new combination regimens may be tested and new indications explored. Through clinical trials, novel treatment options for patients who develop resistance to currently available cancer therapeutics may be developed.

Advances have been made not only in the field of medical oncology but in radiation oncology. Certain biological factors may influence an individual’s response to radiation therapy, leading to variation in therapeutic efficacy and toxicities among patients. The condition of oxygenation and vasculature of both tumour and surrounding normal tissue can determine the effectiveness of radiotherapy. Researchers are attempting to identify biomarkers which can predict the radio-sensitivity of tumour cells and to reduce radiation-induced toxicities in normal tissues. With developments in the field of radiation biology and treatment delivery techniques, it is possible to deliver the right dose of radiation with a high degree of precision to achieve better therapeutic outcome while reducing side effects.

Dr Lee Soo Chin,
Associate Director, Research, NCIS
Medical Spotlight

Ms Joanne Chio heads the Clinical Trials division of Haematology-Oncology Research Group (HORG) at the National University Cancer Institute, Singapore (NCIS). She led a team responsible for conducting Phase I to III clinical trials in cancer endemic in Asia. HORG has led a number of first-in-man and first-in-class early drug studies. Through continuous research, her team has demonstrated that different individuals respond differently to the same drug. This has form the basis of personalised cancer treatment.

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Dr Lee Soo Chin
Dr Lee Soo Chin obtained her medical degrees from the National University of Singapore and the Royal College of Physicians, United Kingdom, and completed a fellowship in cancer genetics at Johns Hopkins School of Medicine, United States. She is currently a Senior Consultant in the Department of Haematology-Oncology and Associate Director, Research at the National University Cancer Institute, Singapore (NCIS). She is also a senior principal investigator at the Cancer Science Institute, Singapore. She specialises in breast cancer and directs the cancer genetics program at the National University Hospital. Her research focus is on breast cancer, pharmacogenetics and cancer genetics, and she is the principal investigator of several multi-centre as well as investigator-initiated breast cancer clinical trials.

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“Whilst the last decade has seen immense strides achieved for our patients with many new, novel and better-tolerated drugs, there is still room for improvement. The era of blindly attempting new cocktails of toxic drugs has essentially ended and we have entered a new phase, with a significant determination to understand the biology, mechanisms and targets concerned as we design relevant clinical trials. Heterogeneity of cancer types, even from the same organ, is now even more clearly considered, which allows for better prognostication and selection of appropriate therapies. Our research efforts at NCIS have embraced this new paradigm of care and the potential to benefit even more of our patients appears more certain to be realised in the coming years.”

Dr Robert Lim,
Senior Consultant,
Department of Haematology-Oncology, NCIS

Trastuzumab (Herceptin) is an example of a group of drugs called monoclonal antibodies. Trastuzumab targets Human Epidermal growth factor Receptor type-2, generally known as HER2/neu receptor, which is over-expressed in 25% of breast cancer and is associated with increased aggressiveness and poor prognosis.

Many patients like Mdm E have benefited from clinical trials evaluating investigational targeted therapies. Many of these investigational drugs have subsequently become standard treatment for different types of cancer, e.g., trastuzumab (breast cancer), rituximab (diffuse large B-cell non-Hodgkins lymphoma), bevacizumab, gefitinib, erlotinib (NSCLC), cetuximab (head and neck cancer), sorafenib (liver cancer), and bevacizumab, cetuximab, panitumumab (colorectal cancer).

The Haematology and Oncology Research Group www.horg.org.sg at the National University Cancer Institute, Singapore www.ncis.com.sg is a leading clinical research group that is actively conducting clinical cancer research in Asia. Many clinical trials have been conducted at our centre in different cancer types, including breast, lung, nasopharynx, gastrointestinal, genitourinary, and hematologic malignancies, to analyse the efficacy and toxicities of new therapeutics. In close collaboration with regional and international academic research institutions and pharmaceutical companies, HORG is one of the leaders in Southeast Asia in conducting early phase cancer clinical trials, including first-in-human and first-in-class trials using novel targeted agents. These trials offer novel treatment options and bring new hope to patients with refractory cancers who have exhausted standard treatment options.
Minimally invasive ("keyhole") techniques are increasingly practised for a myriad of colorectal conditions. These not only include benign conditions like diverticular disease of colon and complete rectal prolapse but also malignant conditions like colorectal cancer. With ample evidence from randomised controlled trials, it is now established that a good oncologic clearance can be achieved via laparoscopic surgery and outcomes are no different from open surgery. With early post-operative advantages such as smaller incisional scars, less post-operative pain and faster recovery with shorter hospital stays, it is no wonder that more patients are asking for keyhole surgery and more surgeons are performing them.

Nevertheless, there are challenges and difficulties in keyhole surgery. Patient factors include complex multi-quadrant abdominal surgery, large inflammatory masses and bulky rectal tumours in the narrow pelvis, especially in males. Surgeon factors often cited are the long learning curve, use of hand-held long shafted instruments and operating whilst standing and craning the neck for long hours. These, however, has changed with the introduction of the surgical robot!

US Food and Drug Administration (FDA) for patient use in general laparoscopic surgery in 2000. The first documented use of the robot was for removal of the gallbladder. Since then, the use of the surgical robot has been extended to various disciplines: urology, gynaecology, cardiothoracic, thyroid, head & neck and now colorectal surgery.

The robotic colorectal surgical program in NUH began in August 2008. We had started with the standard Da Vinci system, retrofitted with a 4th arm (Figure 1). Since January 2010, we have been using a newly acquired Da Vinci Si® system (Intuitive Surgical, Sunnyvale, CA, USA).

The Da Vinci System consists of a surgeon’s console that is in the same room as the patient and a patient-side cart with four robotic arms controlled from the console. Three of the arms are for tools that hold instruments such as scissors, graspers, unipolar, or bipolar electrocautery instruments (Figure 2).
An important feature of the robotic instruments is the Endowrist® function. By designing a “wrist” joint near the end of each instrument, the operator is able to have seven degrees of movement of the instrument tip which translates into increased dexterity in narrow confined spaces. The fourth arm is for an endoscopic camera with two lenses that gives the surgeon full stereoscopic vision from the console. The surgeon will sit at the console and whilst looking through two eye holes at a 3-D image, he will manipulate the robotic arms and the camera with two hand controllers. Foot pedals operate the energy source supplied to the instruments to cauterize, coagulate, or cut the tissue. Foot controls also help to move the endoscopic camera or swop controls of the robotic arms. The robotic system is able to scale, filter and translate the surgeon’s hand movements into precise micro-movements of the instruments, which operate through small incisions in the body.

This provides surgeons with superior visualisation, enhanced dexterity and ergonomic comfort. Therefore, the Da Vinci SI® system makes it possible for more surgeons to perform minimally invasive procedures involving complex dissection or reconstruction especially in difficult-to-access areas.
Over a three-year period between August 2008 and December 2011, a total of 56 robotic colorectal procedures were performed. Two thirds of patients were male, 18% had previous laparotomies, e.g. abdominal hysterectomies, appendectomies and one had a sigmoid colectomy. All but 2 of the patients had cancer. Fifteen (27%) patients received neoadjuvant chemoradiation for locally advanced rectal cancers. The details of surgeries and duration of operation is summarised in Table 1 below.

Table 1: Operative details

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>n=56</th>
<th>Median operating time in minutes (range)</th>
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<tr>
<td>Abdominoperineal Resection</td>
<td>5</td>
<td>476 (256-553)</td>
</tr>
<tr>
<td>Anterior Resection</td>
<td>30</td>
<td>306 (163-485)</td>
</tr>
<tr>
<td>Ultra Low Anterior Resection</td>
<td>17</td>
<td>395 (289-771)</td>
</tr>
<tr>
<td>Sigmoid resection and Recto-</td>
<td>1</td>
<td>315 (315-315)</td>
</tr>
<tr>
<td>pexy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Hemicolectomy</td>
<td>3</td>
<td>286 (204-290)</td>
</tr>
</tbody>
</table>

Although the operating times are longer when compared with standard laparoscopic surgery, this can be due to the increased complexity of the procedures. In some of these patients, standard laparoscopic technique would not have been possible. This is due to the better maneuverability and precision of dissection in confined spaces, best exemplified in the performance of total mesorectal excision for rectal cancer in a deep pelvis. Robotic surgery in these instances has been shown to achieve better surgical margins which would translate to better oncologic outcomes. With a higher precision, there is also better preservation of important nerve structures in the pelvis, avoiding urinary voiding and sexual dysfunction.

It is, therefore, not surprising, for the very benefits mentioned earlier, that this option has been well received by our patients, even though robotic assisted colorectal surgery costs more on average. For patients who will benefit from this technique but has financial difficulties, they would then be considered as beneficiaries from our NCIS Endowment Fund.

NCIS currently has one of the largest robotic-assisted colorectal surgery experiences in Singapore and South East Asia. It is anticipated that the role of surgical robots will continue to evolve and grow in the years to come. With improvements in technology, robotic surgery is predicted to become commonplace and more affordable to the benefit of our patients.

A/Prof Charles Tsang

A/Prof Charles Tsang is the Head and Senior Consultant of the Division of Surgical Oncology at the National University Cancer Institute, Singapore (NCIS). He is also the Associate Director (Clinical) of NCIS. Prof Tsang graduated from NUS in 1987 and obtained his Fellowship Diploma from the Royal College of Surgeons of Edinburgh, Royal College of Physicians and Surgeons of Glasgow, as well as his Master of Medicine (Surgery) from NUS in 1993. He completed a Clinical Fellowship in Surgery in 1994-1995 at the Centre for Digestive Diseases at the Leeds General Infirmary, UK, and went on to the University of Minnesota for an Advanced Residency in Colon & Rectal Surgery. Graduating at the top of his class in 1997, he was the first non-American to be awarded the Carl E Christensen Outstanding Resident Scholar Award.

In 1998, he successfully defended his thesis on Sacral Nerve Modulation for Treatment of fecal Incontinence and was awarded a Master of Science in Experimental Surgery. He returned to Singapore and was a Consultant Surgeon at the Department of Colorectal Surgery at Singapore General Hospital from 1999 before joining NUH and NUS in 2001. Prof Tsang is well-known in endoanal and endorectal ultrasonography for rectal cancer and anorectal diseases and also has a strong interest in the management of advanced colorectal cancer, laparoscopic and robotic surgery.

He is a Visiting Consultant with the Department of Surgery at Ipoh General Hospital and Hospital Selayang in Malaysia, Visiting Professor of Surgery with Korea University Anam Hospital. He is also a Fellow of the Academy of Medicine Singapore, a Governor of the Society of Endoscopic and Laparoscopic Surgeons of Asia and a Fellow of the American Society of Colon & Rectal Surgeons.

A/Prof Dean Koh

A/Prof Dean Koh is a Senior Consultant in the Division of Colorectal Surgery, University Surgical Cluster, at the National University Hospital. He graduated from the medical school at the National University of Singapore and obtained his fellowship diploma from the Royal College of Surgeons of Edinburgh and the Royal College of Physicians and Surgeons of Glasgow. He completed the Joint Specialty Fellowship in General Surgery examination in 2003 and was admitted as a fellow in the Academy of Medicine (Surgery) at the same time.

He then proceeded on to successfully match in the US Accreditation Council for Graduate Medical Education accredited residency programme in Colon and Rectal Surgery at the Ferguson Clinic, Michigan, USA. There, he received formal training in laparoscopic colon and rectal procedures and this remains his main interest in his practice here in Singapore. He is also trained in functional anorectal work and is experienced in endoanal and endorectal ultrasonography. He has been performing robotic-assisted laparoscopic colorectal resections since 2008. He is currently the Director of Minimally Invasive Surgery in the Division of Colorectal Surgery, NUH.

Dr Koh is currently a member of the American Society of Colon and Rectal Surgeons, the Society of Endoscopic and Laparoscopic Society of Asia, and is an Executive Committee Member of the Society of Colorectal Surgeons of Singapore and the Singapore Society of Oncology.

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Colon and rectal cancer stands as the most common cancer in both men and women combined in Singapore. The incidence of this malignancy has been steadily increasing at a rate of approximately 3% since 1968 and has essentially doubled over the past 30 years. From 2003-2007, about 7000 new cases of colon and rectal cancers were diagnosed across the country. The age standardised incidence of this cancer in Singapore stands amongst one of the highest in the world. There is typically a long period in its early development where symptoms are not manifested. And it is during this period that the impact of screening is most pronounced.

The vast majority of colon and rectal cancers arise from adenomatous polyps. The transformation of these adenomatous polyps (adenoma-carcinoma sequence) to cancer has been shown to take 5 to 10 years. This occurs following a series of multiple gene mutations. The key essence is that these adenomatous polyps are relatively asymptomatic. They are present in up to 25% of individuals at the age of 50 years and its prevalence increases with age. More than 90% of these polyps, if detected early by screening modalities, can be removed from the colon without the need for surgery.

This detectable premalignant phase (adenoma), coupled with a relatively long duration of malignant transformation, forms the fundamental basis for screening as an effective means of preventing colon and rectal cancer. Mortality can be reduced simply by screening asymptomatic individuals for the presence of adenomas and early cancers. Studies in the medical literature have demonstrated that the numbers of early staged colorectal cancers detected have been doubled just by instituting an effective screening programme. Reduction of mortality rates of between 15 to 30% has been reported.

The paradigm in screening for colon and rectal cancer has shifted from ‘early detection’ to PREVENTION.

When should screening commence and who should be screened?
Screening in the average risk person should begin at the age of 50 years. This is based on the fact that the risk increases sharply after this age. Screening should commence earlier in increased and high-risk individuals. The age of commencement is dependent on the risk factors present. Increased-risk individuals include those with a personal history of colorectal neoplasia, one or more 1st degree relatives with a history of colorectal cancer, or a personal history of breast, endometrial or ovarian cancers. High-risk individuals are those who possess a hereditary or inherited predisposition to developing colorectal cancers. These include those who have a family history of one of the polyposis syndromes. Although uncommon, patients who suffer from a long history of ulcerative colitis are also considered at high risk.

How to screen for colorectal cancer?
For a screening test to be widely applicable, it must be inexpensive, reliable and acceptable. Various screening tests for colorectal cancer have been reported.

Faecal occult blood testing (FOBT) is the only screening modality that has been shown, in 3 large randomised trials, to show a 33% reduction in colorectal cancer mortality. In light of this, there is very little reason not to offer FOBT screening for average risk individuals aged 50 years and above at the very least. It is important to note that the early studies mentioned above made use of the guaiac-based kit which has been shown to have a 60-70% sensitivity for cancer and only 25-50% sensitivity for polyps.

Nowadays, most FOBT kits utilise the faecal immunochemical test (FIT). This has been shown to be more sensitive and technologically superior. The hallmark of this is that it is specific for human globulin, thereby reducing the incidence of false positives from red meat ingestion. It is more specific for sources of bleeding in the lower gastrointestinal tract. To top it off, the method of collection is far simpler and should increase compliance. Head to head comparisons between FOBT and FIT have shown the latter to be superior in sensitivity for both cancers and polyps. The recommendation for FIT is for 2 separate samples to be taken on 2 separate days.

A positive FOBT or FIT mandates further evaluation with optical colonoscopy.

Optical colonoscopy
This is the only test that allows for the direct visualisation of the colonic mucosa. It is by far the most accurate means of diagnosing colon and rectal neoplasia and serves as the gold standard by which all other screening modalities are referenced. The main advantage of colonoscopy is the fact that it remains the only means by which polyps can be removed at the same seating as the diagnostic procedure. The removal of these polyps essentially prevents them from ever developing into cancer. Another benefit of colonoscopy is the long recommended screening interval of 10 years.
Pre-procedure bowel preparation usually takes 1 of 2 forms: 1) high-volume (3-4 litres) polyethylene glycol (PEG), or, 2) low-volume (90 mls) oral fleet. Oral fleet is contra-indicated in patients with renal impairment due to its high phosphate content. For suitable patients, it is a more palatable option as it can be mixed with sweetened fluids. Patients taking oral fleet must be encouraged to drink plenty of water to decrease the likelihood of phosphate toxicity.

The reported miss rates for optical colonoscopy are between 6% and 12% for large adenomas, and 5% for cancers. More often than not, it is the small, flat polyps that are missed. New imaging modalities such as chromoendoscopy, narrow band imaging and other adjunct technologies have been developed to increase and improve the yield of polyp detection during the procedure.

The screening interval for colonoscopy is dependent on the findings at the index procedure. The 10-year interval is applicable only if there were no neoplastic lesions found. This interval drops with increasing numbers and complexity of the polyps detected. Colonoscopy is the only screening test that combines detection with prevention by polypectomy. A note on flexible sigmoidoscopy should be made. Its main difference is that no prior mechanical bowel preparation aside from fleet enemas is required. Its effectiveness is based on the assumption that two-thirds of polyps and cancers are located within the reach of the sigmoidoscope. It is prudent to note that about 60% of advanced neoplastic lesions are not associated with a distal lesion. Hence, the recommendation is that sigmoidoscopy should be combined with faecal occult blood testing for better detection.

### Table – Recommendations for screening of colon and rectal cancer

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>SCREENING TOOL</th>
<th>ONSET</th>
<th>FREQUENCY</th>
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<tbody>
<tr>
<td><strong>A. Average risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic or family history limited to non-first degree relatives</td>
<td>Faecal occult blood testing</td>
<td>50 years</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy</td>
<td>50 years</td>
<td>Every 10 years</td>
</tr>
<tr>
<td></td>
<td>CT Colonography</td>
<td>50 years</td>
<td>Every 5 years</td>
</tr>
<tr>
<td><strong>B. Increased risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Colorectal cancer in first degree relative age 60 years or younger or two or more first degree relatives</td>
<td>Colonoscopy</td>
<td>10 years prior to youngest case in the family or age 40 years, whichever is earlier</td>
<td>Every 5 years</td>
</tr>
<tr>
<td>2. Colorectal cancer in first degree relative over the age of 60 years</td>
<td>Colonoscopy</td>
<td>10 years prior to youngest case in the family or age 50 years, whichever is earlier</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>3. Personal history of colorectal polyps</td>
<td>Colonoscopy</td>
<td>3 years after polypectomy in the presence of high risk features (&gt;1 cm, multiple, villous architecture); otherwise, 5 years after polypectomy for low risk polyps</td>
<td>—</td>
</tr>
<tr>
<td>4. Personal history of colorectal malignancy</td>
<td>Colonoscopy</td>
<td>One year after resection</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>5. Personal history of ovarian or endometrial cancer</td>
<td>Colonoscopy</td>
<td>One year after resection</td>
<td>—</td>
</tr>
<tr>
<td><strong>C. High risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Family history of familial adenomatous polyposis</td>
<td>Flexible sigmoidoscopy (switch to colonoscopy if adenomas identified); consider genetic counselling and testing</td>
<td>10 to 12 years (from puberty)</td>
<td>Annually</td>
</tr>
<tr>
<td>2. Family history of hereditary non-polyposis colorectal cancer</td>
<td>Colonoscopy; consider genetic counselling and testing</td>
<td>20-25 years</td>
<td>Every 1-2 years</td>
</tr>
<tr>
<td>3. Inflammatory bowel disease</td>
<td>Colonoscopy</td>
<td>From 15th year of diagnosis onwards</td>
<td>Every 1-2 years</td>
</tr>
<tr>
<td>a. left-sided colitis</td>
<td>Colonoscopy</td>
<td>From 8th year diagnosis onwards</td>
<td>Every 1-2 years</td>
</tr>
<tr>
<td>b. pan-colitis</td>
<td>Colonoscopy</td>
<td></td>
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</table>
Virtual colonoscopy is a minimally invasive imaging examination using a new radiologic technique to generate images of the colon and rectal wall. Rapid advancements in this technology, including multi-detector CT, thin slices, software improvements and techniques such as stool tagging with barium or contrast agents have made this the best available imaging test if optical colonoscopy is contraindicated or incomplete. There is, however, still the existing concern with the risk of cumulative radiation if used repetitively for surveillance.

Full mechanical bowel preparation similar to that for colonoscopy is still a requirement. More importantly, there will still be a need to undergo optical colonoscopy to rule out suspicious lesions and for therapeutic polypectomy. The current recommended interval for this modality is 5 years if the results are normal.

**Note for other tests**

Double contrast barium enema, whilst commonly employed in the past, is no longer recommended as a first-line modality for colorectal cancer screening. It is still an option if colonoscopy is contraindicated or unsuccessful. Stool DNA tests are still not ready for population screening due to the lack of standardised laboratory protocols, the high costs of tests, and the lack of data on appropriate intervals between negative stool DNA examinations.

Lastly, whilst serum carcinoembryonic antigen (CEA) is useful for monitoring tumour burden in patients already diagnosed with colorectal cancer, its low specificity and sensitivity in the diagnosis of colorectal cancer makes it a poor screening tool.
Palliative Care for Cancer – When, Where, How?

Dr Noreen Chan, Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS)

The World Health Organisation defines Palliative Care as “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”

Although from its earliest days, palliative care has been closely linked to cancer, many patients do not access palliative care services until very late in their disease course. There are many reasons for this, not least the misperception that palliative care equals “End of Life Care”, thus discouraging physicians from referring, and patients and families from accepting.

In fact, palliative care is part of multi-disciplinary and comprehensive cancer care, offering an “extra layer of care” alongside any cancer-directed therapy. It has a role at any stage of the disease, including at the time of diagnosis.

Nowhere is this paradigm shift more evident than the recent release of a new Provisional Clinical Opinion by the American Society of Clinical Oncology (ASCO) entitled “The Integration of Palliative Care into Standard Oncology Care”. Seven published randomised clinical trials (RCTs) formed the basis of the “Panel’s expert consensus that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.”

The main impetus for this practice-changing recommendation is the study by Dr Jennifer Temel3 and colleagues, published in the New England Journal of Medicine (NEJM) in August 2010. The study showed that patients who were randomised to palliative care plus standard therapy for metastatic non-small cell lung cancer (NSCLC) had significantly longer overall survival than did patients randomised to standard care alone, (11.6 vs. 8.9 months, P = .02), even though the palliative care group had less aggressive end-of-life care.

Although a survival benefit was not a planned-for outcome, the fact that patients not only had better quality of life and less depression, but were also possibly living longer, caught the attention of many.

So what is it exactly about palliative care that made a difference? Two subsequent papers, based on the Temel et al, study, have attempted to shed light on the matter. One by Jacobsen et al.4 analysed 67 consultations by seven palliative care physicians who had participated in the trial. Initial consultations were typically about an hour long and largely focused on symptom management, patient and family coping, and illness understanding, and education. If a patient had lower quality of life scores on assessment, the consultation – not surprisingly – took longer, and the extra time would be spent on symptom management.

In February 2012 the Journal of Clinical Oncology published a secondary analysis5 of the frequency and timing of IV chemotherapy use in the 151 patients who had participated in the trial of early palliative care versus standard care. The overall numbers of chemotherapy regimens did not differ significantly between the groups. But the group which received early palliative care was more likely to have discontinued chemotherapy within 60 days of death.

Of course, the findings from this study are from a single setting and looked only at outpatient clinic consultations, and may not be generalisable; but a few important conclusions can be drawn: palliative care introduced early does not shorten survival, and palliative care is not high-tech but seems to produce measurable benefits.

The Supportive & Palliative Care Group @ NCIS

The National University Cancer Institute, Singapore (NCIS) has had a palliative care service since 2008, offering outpatient clinic consultations as well as a multi-disciplinary consultative service to inpatients of the National University Hospital (NUH). The inpatient service serves the whole hospital, regardless of diagnosis and age, so patients with non-cancer diagnoses, as well as children, are seen.

Within NCIS, a multi-disciplinary Supportive and Palliative Care group has been set up, in recognition of the fact that the cancer journey is not just a physical one, and that patients may require psycho-emotional, social and/or spiritual support. Working with oncologists, nursing, allied health and volunteers, as well as community-based services like hospice home care, this groups aims to integrate supportive and palliative care into comprehensive cancer care.
**H’s story:**

H is a 45-year-old man who was diagnosed with locally advanced Non-small cell Lung Cancer (NSCLC) in 2011, presenting as axilla and upper chest wall pain. This was a severe neuropathic pain typical of a Pancoast (apical lung) tumour that had invaded the upper ribs and intercostals nerves.

He was referred to Palliative Medicine at the same time as he was commencing his concurrent chemotherapy-radiotherapy treatment. His pain was managed with a combination of morphine and nortriptyline, and much time was spent in discussion and education about lifestyle changes (including diet and exercise), as well as coping with the cancer diagnosis and treatment.

About two weeks after completion of the chemo-RT, during his regular Palliative Medicine clinic follow-up, he reported improved pain control and the decision was made to start reducing his analgesia. But he was also noted to have lost about 3kg of weight, and further questioning revealed that he was having trouble swallowing. This was consistent with radiation oesophagitis; a quick telephone call to the radiation oncologist confirmed the situation, and H was started on some Mylocaine® and given some dietary advice (including suggestions for liquid supplements).

H is still attending the Palliative Medicine clinic. His pain is much better, although he requires ongoing low dose nortriptyline at night. Although his follow up CT scan had shown only a partial response, he is nonetheless a “cancer survivor” and has been encouraged to resume work. With our support and that of his family and friends, he has tried to turn his cancer journey into one of personal and spiritual growth. H’s journey is far from over, and he lives every day with the shadow that the cancer could flare up, but he also knows that whatever happens, he will not be alone.

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**Dr Noreen Chan**

Dr Noreen Chan serves as Senior Consultant in the Department of Haematology-Oncology at the National University Cancer Institute, Singapore (NCIS), where she leads the Palliative Care service for the National University Hospital. She is also Director (Education) of the Lien Centre for Palliative Care.

She received her training in England, Singapore and Australia and her interests include the interface between Oncology and Palliative Care; Ethical issues and Decision-making at the End of Life; and Education in Palliative Care at all levels.

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Peritoneal carcinomatosis is a condition whereby there is transcoelomic spread and dissemination of cancer cells intra-abdominally within the peritoneal cavity. Clinical presentation may be insidious – abdominal discomfort with distension, ascites, palpable masses intra-abdominally, or, may be diagnosed only at the time of laparotomy or laparoscopy. Imaging such as CT scans may reveal omental caking with peritoneal masses and ascites. Whatever the presentation, the findings of peritoneal carcinomatosis is often associated with terminal malignancy and a poor prognosis, and hence, treatment, is often palliative in intent, aimed at relieving symptoms, such as obstruction and ascites.

More recently, there has been a radical shift in the approach to managing patients with peritoneal carcinomatosis. This approach comprises 2 components. Firstly, there is radical surgical cytoreduction (CRS) by visceral resection and peritonectomy procedures with the aim of removing all grossly visible tumours. Secondly, surgery is followed by Hyperthermic intraperitoneal chemoperfusion (HIPEC), which is aimed at residual microscopic disease.

The different chemotherapy agents used are hydrophilic and have a large molecule size to concentrate them within the peritoneal cavity for maximum local therapeutic effect. The chemotherapy agents are also heated to 43°C (hyperthermic), which potentiates the cytotoxic effect via direct and indirect mechanisms. CRS and HIPEC are currently being used to treat peritoneal carcinomatosis from appendiceal, colorectal, ovarian, gastric cancers, sarcomas, primary peritoneal carcinomatosis and primary mesotheliomas.

Peritoneal cancer index (PCI) (Figure 1) is an important prognostic marker other than completeness of cytoreduction after surgical resection (CCR Score) (Figure 2). Median survival rates of 41 months have been reported in patients with a favorable PCI of <16. In patients where complete cytoreduction has been achieved (CCR-0), the median survival was 32.4 months (vs. median survival of 8.4 months for CCR-1). Patients with extended carcinomatosis also fared better than patients with limited disease (33% 5Y actuarial survival vs. 11%). This is not surprising as outcomes are related to disease burden and effectiveness in removing and eliminating any residual malignant cells. To date, there has been only one randomised controlled trial with a long-term follow-up of 8 years comparing CRS & HIPEC vs. systemic chemotherapy & palliative surgery. There was disease specific survival advantage in patients who underwent CRS & HIPEC (median survival of 22.2 months vs. 12.6 months in standard treatment arm). In a subset analysis, completeness of cytoreduction was also a prognostic factor with a 5Y survival of 45% seen in patients where a R1 resection was achieved.

Given the radicality and complexity of the procedure, morbidity and mortality rates of 20-50% and 1-10% respectively have been reported. Factors affecting morbidity are duration of surgery, extent of disease and number of anastomoses performed. Hence, careful patient selection is necessary.
A/Prof Dean Koh

A/Prof Dean Koh is a Senior Consultant in the Division of Colorectal Surgery, University Surgical Cluster, at the National University Hospital. He graduated from the medical school at the National University of Singapore and obtained his fellowship diploma from the Royal College of Surgeons of Edinburgh and the Royal College of Physicians and Surgeons of Glasgow. He completed the Joint Specialty Fellowship in General Surgery examination in 2003 and was admitted as a fellow in the Academy of Medicine (Surgery) at the same time. He then proceeded on to successfully match in the US Accreditation Council for Graduate Medical Education accredited residency programme in Colon and Rectal Surgery at the Ferguson Clinic, Michigan, USA. There, he received formal training in laparoscopic colon and rectal procedures and this remains his main interest in his practice here in Singapore. He is also trained in functional anorectal work and is experienced in endoanal and endorectal ultrasonography. He has been performing robotic-assisted laparoscopic colorectal resections since 2008. He is currently the Director of Minimally Invasive Surgery in the Division of Colorectal Surgery, NUH.

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A/Prof Charles Tsang

A/Prof Charles Tsang is the Head and Senior Consultant of the Division of Surgical Oncology at the National University Cancer Institute, Singapore (NCIS). He is also the Associate Director (Clinical) of NCIS. Prof Tsang graduated from NUS in 1987 and obtained his Fellowship Diploma from the Royal College of Surgeons of Edinburgh, Royal College of Physicians and Surgeons of Glasgow, as well as his Master of Medicine (Surgery) from NUS in 1993. He completed a Clinical Fellowship in Surgery in 1994-1995 at the Centre for Digestive Diseases at the Leeds General Infirmary, UK, and went on to the University of Minnesota for an Advanced Residency in Colon & Rectal Surgery. Graduating at the top of his class in 1997, he was the first non-American to be awarded the Carl E. Christensen Outstanding Resident Scholar Award. In 1998, he successfully defended his thesis on Sacral Nerve Modulation for Treatment of fecal Incontinence and was awarded a Master of Science in Experimental Surgery. He returned to Singapore and was a Consultant Surgeon at the Department of Colorectal Surgery at Singapore General Hospital from 1999 before joining NUH and NUS in 2001. Prof Tsang is well-known in endoanal and endorectal ultrasonography for rectal cancer and anorectal diseases and also has a strong interest in the management of advanced colorectal cancer, laparoscopic and robotic surgery. He is a Visiting Consultant with the Department of Surgery at Ipoh General Hospital and Hospital Selayang in Malaysia, Visiting Professor of Surgery with Korea University Anam Hospital. He is also a Fellow of the Academy of Medicine Singapore, a Governor of the Society of Endoscopic and Laparoscopic Surgeons of Asia and a Fellow of the American Society of Colon & Rectal Surgeons.

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Success is measured by the percentage of complete cytoreductions, and is achieved in high volume centres. It takes approximately 130 procedures to reach the peak of the learning curve.

Cost implications are considerable and range from S$55,000 – S$80,000 depending on the complexity of surgery, and length of stay in the intensive care ward and the hospital. Our average length of stay so far has been 2 weeks. Most countries approve the treatment on a case-by-case basis. Standardised guidelines are still scarce and current recommendations conclude that HIPEC in conjunction with CRS is of value in carefully selected patients only.
Stereotactic body radiation therapy (SBRT) is a newly-developed cancer treatment technology. Utilising specialised and highly advanced equipment, software and procedures, a tumour’s location is precisely defined, and its size and shaped exactly mapped. Then, during the treatment itself, the patient is precisely positioned, immobilised, and administered high-precision, high-dosage external radiation therapy.

“Stereotactic” stems from the Greek “stereo” (solid) and “taxis” (arrangement, order). The term “stereotactic” refers to a surgical technique for precisely directing a delicate instrument or beam of radiation, using three-plane coordinates provided by medical imaging (computed tomography, for example).

The technology allows intensely focused and highly precise treatment of the target area, with minimal effect on surrounding, healthy tissue.

Though stereotactic surgery was originally developed for use in cranial surgery, technological advances now permit us to employ similar techniques to treat the lungs, liver, spine and other organs and areas of the body.

SBRT involves delivery of a single, high-dosage radiation treatment, or a short series of fractionated treatments. The therapeutic radiation is delivered with a precision and dosage not previously attainable using conventional radiation therapy. The result has been a marked and encouraging improvement in treatment success rates.

SBRT works similarly to other forms of radiation treatment, in that it damages the DNA of tumour cells (rather than removing the cells completely). The irradiated cells lose their ability to reproduce, leading to shrinkage and eventual disappearance of the cancerous mass. Benign tumours treated with SBRT ordinarily vanish over a period of a year and a half to two years. In the case of malignant or metastatic tumours, shrinkage is often even more rapid, sometimes taking little as just a few months.

SBRT differs from conventional radiotherapy primarily in the precision of radiation delivery. Expert radiation oncologists and their teams, specialised in the technique, use multiple, converging beam angles to safely deliver high-potency dosages, with a very steep dosage gradient outside the target tissue. Surrounding, healthy tissue is almost entirely unaffected.

In SBRT, some centres – including ours at NCIS – are equipped to add a fourth dimension to the three traditionally used in stereotactic procedures, for even greater accuracy. Specifically, pre-treatment imaging and planning include sampling and mapping the body’s motions at the tumour site, so that these can be compensated for while radiation is being delivered to the area. Although not all centres employ 4D CT simulation in the SBRT treatment process, this step is a routine part of our SBRT procedure.

A complete course of SBRT treatment is also significantly shorter than conventional fractionated radiotherapy. In many cases, only a single treatment is required. In others, from two to five fractionated treatments may be indicated – but even here the entire course of treatment is ordinarily completed in from one to two weeks. All of this means greater convenience for the patient, and minimises delay or disruption of systemic therapy.
Insight

What cancer sites may be treated with SBRT?
At NCIS, SBRT’s main use at the present is in the treatment of tumours in two areas: the lungs and the liver.

Lungs
In treating primary cancer of the lungs, SBRT is most useful for:
- Patients with small lung tumours (up to 5 cm)
- Patients who are medically unfit for radical surgery
- Patients who decline surgery

SBRT may also be used in treating cancers, which have metastasised to the lungs, where the patient has up to three lung nodules.

Liver
SBRT is useful in treating hepatocellular carcinoma in:
- Patients judged medically unfit for surgery
- Patients who are not suitable for, or who have failed TACE treatment.
- Where cancer has metastasised to the liver, SBRT may be used in treating:
  - Patients with up to three metastatic liver nodules
  - Patients with a tumour smaller than 6 cm
  - Patients with limited active disease elsewhere in the body

Other cancers, intra-abdominal and beyond
Use of SBRT is also expanding to treatment of cancers in other areas. Pancreatic cancer, renal cancer and retroperitoneal sarcoma are prime examples, along with tumours located in the head, neck, prostate, or, in close proximity to the spinal cord. For certain tumours in the brain, SBRT or stereotactic radiosurgery (SRS) can be used.

SRS is a technology similar to SBRT, but the total radiation dose is only delivered over a single session. As research goes forward, it is highly likely that use of SBRT will broaden even further. Because of the extreme precision it affords, as well as its other advantages, its future as a preferred cancer treatment modality is promising indeed.

Advantages of SBRT over other treatment options
When SBRT was first introduced, it was primarily intended for treatment of patients with early-stage lung cancer. In the past, treatment of such patients involved radical lobectomy (removal of one or more lung lobes). In some cases, affected mediastinal lymph nodes were also removed. Because lung cancer patients are frequently smokers, and many are elderly, a significant proportion of those seeking treatment were not keen on submitting to radical surgery. Some of these patients were offered radical external-beam radiation therapy as an alternative treatment; however, even this option was strenuous. RT usually involves seven weeks of daily external beam radiotherapy – an average of 35 sessions, each lasting about 30 minutes. From preparation to completion, the full course of RT treatment is approximately two months.

With SBRT, however:
1. Treatment outcome for eligible and properly selected patients appears similar to surgery, and certainly much better than external beam radiotherapy using conventional fractionation and technology
2. Treatment duration is reduced to just one to five sessions, each lasting about 45-60 minutes. Total treatment duration inclusive of preparation is about two weeks – a reduction of roughly 80%, compared to traditional RT treatment.

3. Side effects – dependent on tumour location – are relatively mild in carefully selected patients. Patients experience less lethargy, esophagitis, and risk of pneumonitis.

4. Overall cost of SBRT is slightly higher than conventional treatment. However, for Singaporeans, a significant proportion of the cost can be subsidised by Medisave and/or Medishield.

SBRT appears to be an attractive treatment option, particularly for patients who are often either poor surgical candidates, or very reluctant to undergo surgery. SBRT is also well worth considering for patients who do not wish to travel to and from the hospital daily, for nearly two months of external beam radiation treatment.

SBRT also has a high appeal to foreign patients, who would need to spend significantly less time in the country for treatment.

Additionally, because of the relatively small amount of time required for a full course of SBRT treatment, machines, personnel and facilities may be utilised to treat a greater number of patients within a given period. This factor means reduced waiting time for patients wishing to begin treatment.

SBRT has also been used in treating oligometastatic disease. For some stage four diseases, such as colorectal and renal cell cancers, removal of metastatic tumours may provide better overall survival. Also, in cases where systemic control of the disease is excellent, but solitary residual tumours exist, SBRT may be useful in treating the oligometastatic or residual disease.

What patients can expect
Following is an outline of the various steps your patient can expect to experience prior to, during, and following SBRT treatment at NCIS.

1. Evaluation and patient selection
The patient’s history is reviewed, and his or her case evaluated as to suitability for SBRT. The evaluation includes:

**Patient factors**
- Physical condition, including ECOG status, ability to lie still and to comply with instructions
- Lung function (if treating the lung)
- Liver function (Child-Pugh grading, if treating the liver)

**Disease factors**
- Size and location of tumour (tumour smaller than a certain size as defined in current protocols, and situated at a safe and suitable distance from critical organs)
- Extent and control of systemic disease (mainly for oligometastasis and good systemic disease control)
- Disease progression (how rapidly disease progressed following initial diagnosis)
- Previous patient history of radiotherapy

2. Patient Consent
The full procedure will be explained to the patient, including possible risks, discomforts, side effects and alternative treatment options. The patient’s understanding of these points is consulted, and written consent to proceed is obtained, according to standard protocols and requirements.

3. Four-dimensional Computed Tomography (4D CT) simulation
Computed tomography simulation is required for planning of the SBRT treatment, with the patient in the treatment position.

The patient is placed in the supine position, in an immobilisation device and in the exact position that will be used during actual treatment. Though the immobilisation device restricts body movement, the patient is still able to breathe normally.

4D CT simulation is carried out. CT scan images are taken during multiple respiratory cycles, so that the tumour’s exact range and pattern of movement during normal respiration can be mapped and recorded. During actual SBRT treatment, this information is used in guiding delivery of radiation dosages with extreme accuracy, for maximum treatment effectiveness and minimum affect on neighbouring tissues.

Once the CT simulation has been completed, small, permanent marks are made on the patient’s body. These will help in accurately positioning the patient at the time of treatment.

With this step completed, the patient is ordinarily scheduled for treatment, and then sent home.
4. Planning
Planning is one of the most critical steps in the entire process of SBRT, although the patient is not present for this phase. The patient's 4D CT images are imported to the planning software, and the tumour planning target volume (PTV) and normal-tissue organs are contoured. A treatment plan is produced, aimed at delivering the maximum prescribed radiation dose to the PTV, with rapid dose fall-off to the surrounding normal tissues. This is the exact beauty of SBRT - extremely high doses of radiation can be delivered precisely to the planned target volume, while sparing normal tissues.

Other imaging modalities may be incorporated at this stage, where available and applicable. These can include MRI, PET, and other novel imaging procedures and protocols.

5. Quality Assurance
A series of procedures is now conducted to ensure the quality, accuracy and safety of procedural planning. This step utilises various high-tech devices and advanced software. This step is essential in the delivery of SBRT as it ensures the quality of the approved plan and the safety of the delivery of the intended radiation dose to the target volume while maintaining minimal radiation dose to the surrounding normal tissues. This quality assurance is performed in addition to the stringent quality assurance process scheduled for all our treatment machines. Our dedicated medical physicist performs patient-specific quality assurance before each patient undergoes his first SBRT session. As very high doses of radiation are delivered to the patient each SBRT session, we dedicate extra measures to ensure patient safety.

6. Treatment
Depending upon the treatment plan generated in the preceding steps, the patient is scheduled for from one to five treatment sessions. If multiple sessions are needed, they are scheduled over a one- to two-week period.

There are normally no restrictions on eating or drinking before the procedure, though some patients may be given anti-inflammatory, anti-nausea or anti-anxiety medication prior to the treatment. (If the attending physician determines that eating or drinking should be restricted for a period prior to treatment, the patient will be informed of this well in advance).

The patient is consulted and counselled before each treatment, and his status reviewed.

Once the patient has been positioned, and before the actual treatment is administered, a cone beam computed tomography scan (CBCT) is done, for final confirmation of the tumour's position and dimensions.

During the treatment itself, our SBRT radiation oncologists and medical physicists will be at the treatment console, utilising all available on-board imaging technologies to deliver the treatment in close accordance with the original treatment plan. They also take into account all potential patient-specific, tumour-specific, and organ-specific motion during treatments, in real time.

The patient is awake throughout the procedure, and can expect to complete the treatment without pain.

The entire procedure can take up to an hour.

SBRT is usually performed on an outpatient basis, but the patient should be prepared to spend up to a half a day at our facility. Patients will be informed in advance whether they will need to have someone on hand to drive them home, following their treatment.

In most cases, SBRT patients can resume all their normal activities within a day or two after treatment.

7. Follow-up
Once treatment is complete, the patient will be scheduled for routine follow-up consultations. Follow-up scans and investigations will also be arranged, to evaluate results and response to treatment, as well as any possible side effects.

8. Side Effects
Side effects of any radiation treatment can be the result of the treatment itself, or due to possible damage to healthy cells near the treatment area. The patient will be briefed on potential side effects before the procedure, as part of the education and consent process. In follow-up visits, the patient will be asked if any side effects or reactions have been noticed, and will be given assistance in managing any that may occur.

There are sometimes side effects, which become evident during or immediately after radiation therapy, but these ordinarily disappear within a few weeks, at most. These can include tiredness, fatigue and skin reactions. Skin in the treated area may become more sensitive, red and dry. Dry, itching, blistering or peeling skin are rarely experienced. Again, any such effects are ordinarily quite temporary.
Other, less common early side effects (depending somewhat on the area treated) may include chest pain and shortness of breath.

Rarely, there may be side effects that do not appear for months or years after the completion of treatment. Depending on the site treated, these can include brain or spinal cord changes, lung changes, or secondary cancer.

The risk of developing cancer as a result of radiation therapy is very small. Nonetheless, following treatment, the patient should be checked regularly by a radiation oncologist for signs of recurring or new cancerous growth.

**Clinical trials in SBRT**

Clinical trials in radiation therapy are often available, aimed at discovering, evaluating and developing new and better treatment approaches and strategies.

During the patient's initial visit, the attending physician will discuss any current and applicable clinical trials. If the patient wishes to participate, the specific trial's various steps and requirements will be included in the course of treatment – from consent, through treatment and follow-up.

More information on clinical trials can be found at the Haematology Oncology Research Group's (HORG) website: [http://www.horg.org.sg](http://www.horg.org.sg)

**What the Physician can expect**

As a referring physician, you can depend on NCIS to work closely with you in providing your patient with the finest treatment and continuing care possible. We will keep you well informed on our findings, the treatment itself, its results, and the findings of all follow-up visits, consultations, tests and imaging. We respect and value your knowledge of and relationship with the patient, and your partnership in care.

**Conclusion**

SBRT represents a powerful new weapon in the cancer-treatment arsenal at the National University Cancer Institute (NCIS) and its Radiation Therapy Centre. Through its use, SBRT specialists are maximising the cancer-destroying capabilities of radiation treatment while minimising its effect on healthy tissues and organs, and the side effects of the treatment itself.
Journey of a Haematologist

Could you share with us why you chose to be a Haematologist? Tell us what would you be doing and where would you be now if you had not become a doctor?

I became interested in haematology while working as a medical officer in Singapore General Hospital’s (SGH) Haematology Department almost 2 decades ago. I was thrilled at the idea that patients with bone marrow failure and leukemia can be cured by bone marrow transplant.

I could still remember a young man who had relapsed Chronic Myeloid Leukaemia (CML) post-bone marrow transplant, being cured by simply giving him lymphocytes harvested from his sibling donor. Without any further chemotherapy his leukaemic cells were completely eradicated.

My senior colleagues enlightened me that this treatment modality, known as donor lymphocyte infusion (DLI), provides the strong evidence that cancer cells can be eradicated via an immunological effect of the T lymphocytes called graft-versus-leukemia. That moment was like a lightning bolt for me: I witnessed the application of basic immunology to the field of clinical transplantation and in the treatment of cancer.

From that day on, I knew that clinical haematopoietic cell transplantation was where I was going. Haematology is a field that places big demands on its staff. Despite the difficulties, it is an exciting, cutting-edge specialty where we can make a huge difference in peoples’ lives. Also, the “imperfection” of the art and science, because there is so much that we do not yet understand, is an intellectual challenge.

Dr Koh is a Senior Consultant at the Department of Haematology-Oncology. After receiving his undergraduate medical degree from the National University of Singapore, he continued his internal medicine training before obtaining his membership from the Royal College of Physicians of the United Kingdom. He then undertook his advanced specialist training in haematology before pursuing his training in haematopoietic stem cell transplantation under the Adult Bone Marrow Transplant (BMT) Program at the Duke University Medical Center in USA. His research interest focuses mainly on clinical haematopoietic stem cell and umbilical cord blood transplantation for adults with haematological diseases.
I am not sure what I would be doing if I had not become a doctor. I had a deep interest in physics during my secondary school days; hence I may consider majoring in physics in university had I not been accepted by medical school. As a teenager, I used to idolise Dr Richard Feynman, an American physicist and Nobel laureate in 1965, who is well known for his work in quantum mechanics and particle physics. I have read two of his semi-autobiographical books titled “Surely You’re Joking, Mr. Feynman!” and “What Do You Care What Other People Think?”, which I found hilarious and inspiring.

You have particular research interests in stem cell and umbilical cord blood transplantation. What roles do these play in cancer treatment?

Haematopoietic stem cell transplant (HCT) (which includes adult bone marrow/blood stem cell and umbilical cord blood) has been used over the last decades with great success in the management of selected malignant (such as leukemias, myeloma and lymphomas) and non-malignant diseases (such as aplastic anemia) that are otherwise incurable.

The use of HCT has expanded rapidly over the past decades and its role will continue to evolve as advances in conditioning, supportive care, management of complications and expanding stem cell sources further widen its applicability.

What had inspired you to begin your research in these areas?

The field of stem cell transplant remains complex and sophisticated. The transplant specialists are pushing back the boundaries of their knowledge. Day in day out, we are finding new ways to decrease treatment-related toxicity, improve disease control, increase the donor pool, prevent graft versus host disease and apply our therapies for an ever-growing number of diseases.

Our patients now come to us at all ages, with different performance status, with or without co-morbidities, and with early and late diseases. The transplant physicians are now faced with much more challenging decisions: difficulty in deciding the choice of donors and the type of graft (bone marrow versus peripheral blood stem cell, related, unrelated or cord blood), the type of pre-transplant conditioning regimen and intensity etc.

My passion to perform research in this field has been driven by my strong desire to overcome these clinical challenges and to improve our patients’ outcomes.

Helping Cancer Patients

What are some of the newer and exciting developments in Haematology/Oncology that you think have resulted in better treatment for patients?

We have more effective targeted drugs or monoclonal antibodies with less toxicity for various haematological malignancies. This has resulted in better cure rates and improved survival in many of these diseases. In the area of stem cell transplant, with the advent of improved supportive care, reduced-intensity conditioning regimens, and the alternative sources of stem cells, the role of stem cell transplant continues to evolve and has been made more available to more patients in need. Our patients now come to us at all ages, with different performance status, with or without co-morbidities, and with early and late diseases.

Cancer is a very dreaded disease, and there is a certain perception that it is the “death sentence” in life. What’s your personal opinion and advice, and how do you usually motivate your patients in their battle against cancer?

Yes, cancer is certainly formidable and may sound dismal to most people. However, the cure rate and prognosis of many of the once-incurable haematological cancers such as leukemia, lymphoma and myeloma have improved dramatically over the last few decades. This is attributed to the availability of better drugs, treatment regimens and improved supportive care. Notably, in the area of stem cell transplant, the survival of transplant recipients has certainly improved over the years.

I always want my patients to know that they are being taken care of by a team which consists of the most dedicated medical and support staff. Our small corner of medicine is populated by people who are highly trained, incredibly committed to their patients, and trying with all their might to achieve the very best treatment outcomes.
How do you think healthcare professionals, particularly GPs, can help to manage and support cancer patients?
As cancer often presents insidiously, family physicians play a vital link in making early diagnosis of cancer. They can also contribute in providing the support and care of non-cancer health problems (such as diabetes mellitus, hypertension etc).

In haematology patients, the family physicians may also be involved in monitoring the post-treatment blood count of the patients and communicate with the haematologists via phone calls or email. In this way, they can help to reduce the number of hospital visits of these patients and allow them to have some treatments and tests in the community setting.

Personal Memories
Who has had the biggest influence on your career?
It has to be Dr Patrick Tan, who was formerly the head of the Haematology Department at the Singapore General Hospital. He is widely regarded as the pioneer in bone marrow transplant (BMT) in Singapore, and has trained more than half of the BMT physicians locally.

Dr Tan has been an inspiration in motivating me to choose haematology and more specifically, bone marrow transplant medicine, as my career. As a person, he is the perfect gentleman and has never acted unkindly to his subordinates and staff. He is a compassionate doctor and has no qualms about waiving the medical charges of his patients who have financial difficulties. I have been very fortunate to have worked closely with him and to have learnt from his expertise.

Who is the person you admire most?
Dr Nelson Chao, my mentor during my one-year stint at the Duke University Adult Bone Marrow Transplant Programme. Dr Chao is well respected as a leading expert in the area of bone marrow transplant. He is the Programme Director of the Adult Bone Marrow and Stem Cell Transplant Programme.

Under his leadership, the Duke University BMT Program flourished from one which was previously focusing on autologous transplant in breast cancer to what it is today, a leading referral centre with a comprehensive transplant program that encompasses allogeneic, reduced intensity allogeneic transplant, umbilical cord transplant and also one with most extensive experience in haploidentical transplant.

I have always admired Dr Chao’s wealth of knowledge, and his highly acclaimed work in the area of stem cell transplant. More importantly, despite his accolades and outstanding achievements in his area of specialty, Dr Chao remains an approachable, amenable and down-to-earth colleague, mentor and boss. His pleasant disposition is well-regarded by his faculty members, nursing staff and his patients. He also believes strongly in the importance of a well-balanced work and family life.

Could you share with us some memorable experiences or highlights in your career?
It is most gratifying to see many patients with fatal hematological malignancies or bone marrow failure syndrome cured with the modern chemotherapy regimens or stem cell transplant.

We have a stem cell transplant patient reunion that was started 3 years ago. The patients and their family members would gather and share their valuable experiences in this arduous journey in the battle against cancers. Personally, it is very touching for me to see those happy faces of our patients, who were at one stage in their life, struggling with grueling emotional upheaval.

Work-Life Balance
Facing sickness and death daily could be extremely draining. How do you cope with the stresses, and relax in your personal time?
As transplant physicians, we embrace ourselves daily, reminding ourselves that we are tasked to help a group of unfortunate patients in battling their lives against cancers. We accept the immutable fact that some patients do well after chemotherapy or transplant whereas others do not. We treat every treatment failure as an important learning lesson for us to do better for the next patient.

As specialists in this field, we are indeed privileged to treat a very courageous group of patients who have a tremendous stake in our progress thus far, and who have helped in innumerable ways the advancements we have made. It is largely because of a partnership with our patients that outcomes are ever improving, toxicities dramatically decreasing and disease indications expanding.

I usually go for a run around my neighbourhood or on the treadmill after work and during weekends. I try to do this on a regular basis. Not only does it keep me healthy, it also helps to keep me relaxed and reduces some of the work-related anxiety.

Is there anything else you hope to accomplish in 2012?
We hope to expand our adult stem cell transplant programme in NUH, and also try to look at different ways to improve the overall outcome of our transplant recipients. Hopefully we can allow more patients to be cured from their lethal haematological diseases using these ‘life-saving’ cells.
Upcoming Events

NUH GP CME Programme 2012
Please refer to our GPLC website for online registration.

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical Specialty / Topic</th>
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<tbody>
<tr>
<td>2 Jun</td>
<td>Clinical Specialty / Topic</td>
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<tr>
<td></td>
<td>Managing Urological Conditions in Your GP Clinic</td>
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<tr>
<td>30 Jun</td>
<td>Cancer / Surgery</td>
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<td>Management of Breast Cancer - A Comprehensive Approach</td>
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<tr>
<td>7 Jul</td>
<td>Gastroenterology</td>
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<td>Viral Hepatitis in Primary Care</td>
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<tr>
<td>21 Jul</td>
<td>Cancer / O&amp;G</td>
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<td></td>
<td>Gynaecological Cancer Update for GPs</td>
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<td>4 Aug</td>
<td>Cardiology</td>
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<td>Update on Atrial Fibrillation Management</td>
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<tr>
<td>18 Aug</td>
<td>Hand &amp; Reconstructive Microsurgery</td>
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<td>GP Symposium on Fractures of the Hand &amp; Wrist</td>
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Other NUH Events

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<tr>
<th>Date</th>
<th>Clinical Specialty / Topic</th>
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<tbody>
<tr>
<td>24 - 25 Aug</td>
<td>Paediatrics</td>
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<tr>
<td></td>
<td>Wong Hock Boon Paediatric Masterclass 2012</td>
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<tr>
<td></td>
<td>- Kids’ Needs On Wellness (KNOW) Medical Symposium</td>
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</tbody>
</table>

* Event information listed is correct at time of print. While every attempt will be made to ensure that all events will take place as scheduled, the organisers reserve the rights to make appropriate changes should the need arises.

Please refer to our events calendar at www.nuh.com.sg/nuh_gplc/index/index.htm for more updates and information.

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