

# MEDICAL NEWS

A SingHealth Newsletter for Medical Practitioners MCI (P) 024/11/2015



## FOCUS: CANCER

Improving Survival Outcomes in Liver Cancer

The Art of Precision – Modern External Beam Radiotherapy

“Catching Cancer” – Head & Neck Cancer and Multidisciplinary Care





# Improving Survival Outcomes in Liver Cancer

Prof Pierce Chow, Senior Consultant, Division of Surgical Oncology; Co-Director (Surgical), Comprehensive Liver Cancer Clinic, National Cancer Centre Singapore

Academic Medical Program (Oncology), Duke-NUS Medical School

## THE BURDEN AND CLINICAL OUTCOMES OF LIVER CANCER

Primary Liver Cancer or HCC (Hepatocellular Carcinoma) is endemic to the Asia-Pacific which shoulders almost 80% of the burden of this cancer worldwide. This is due to the high prevalence of chronic viral hepatitis B in our part of the world. Overall survival in advanced HCC is grave although outcomes have improved with recent advances in therapeutics.

When discovered in its early stages however, surgical resection for HCC confers potential cure. For HCC diagnosed at an early stage, defined as HCC within the Milan Criteria or BCLC Stage A (single lesion < 5 cm or 3 lesions or less each < 3 cm), a 5-year median overall survival of more than 60% is achievable.

Surgical resection is possible for some intermediate-stage HCC beyond the Milan Criteria but with understandably poorer overall survival. Unfortunately, surgical resection may not even be possible with many such patients.

Down-staging of intermediate-stage cancers to an earlier stage cancer before surgical resection is an established practice for many solid cancers including common cancers like breast and colorectal cancers. Currently available therapeutics for intermediate-stage breast and colorectal cancers are highly efficacious and the concept of neo-adjuvant therapy in these cancers before resection is thus feasible.

Unfortunately, previously available therapeutics for intermediate-stage HCC have not been very efficacious. Down-staging of intermediate-stage HCC to resection is not an established practice in HCC.

## LOCO-REGIONAL THERAPY WITH SELECTIVE INTERNAL RADIATION THERAPY (SIRT) IN LIVER CANCER

Following a successful phase II clinical trial of Selective Internal Radiation Therapy (SIRT) for HCC that we published in 2014 (AHCC05 SirSA), SIRT with yttrium-90 is currently routinely used at the National Cancer Centre Singapore (NCCS) for treatment of intermediate-stage and advanced stage HCC. This is carried out in collaboration with our Nuclear Medicine physician and Interventional Radiologist colleagues at the Singapore General Hospital (SGH).

During SIRT, tiny microspheres coated with the radioactive nuclide yttrium-90 is introduced via an artery directly into the liver cancer. Yttrium-90 emits short range but powerful beta-radiation and is ideal for such radiation therapy known as brachytherapy.

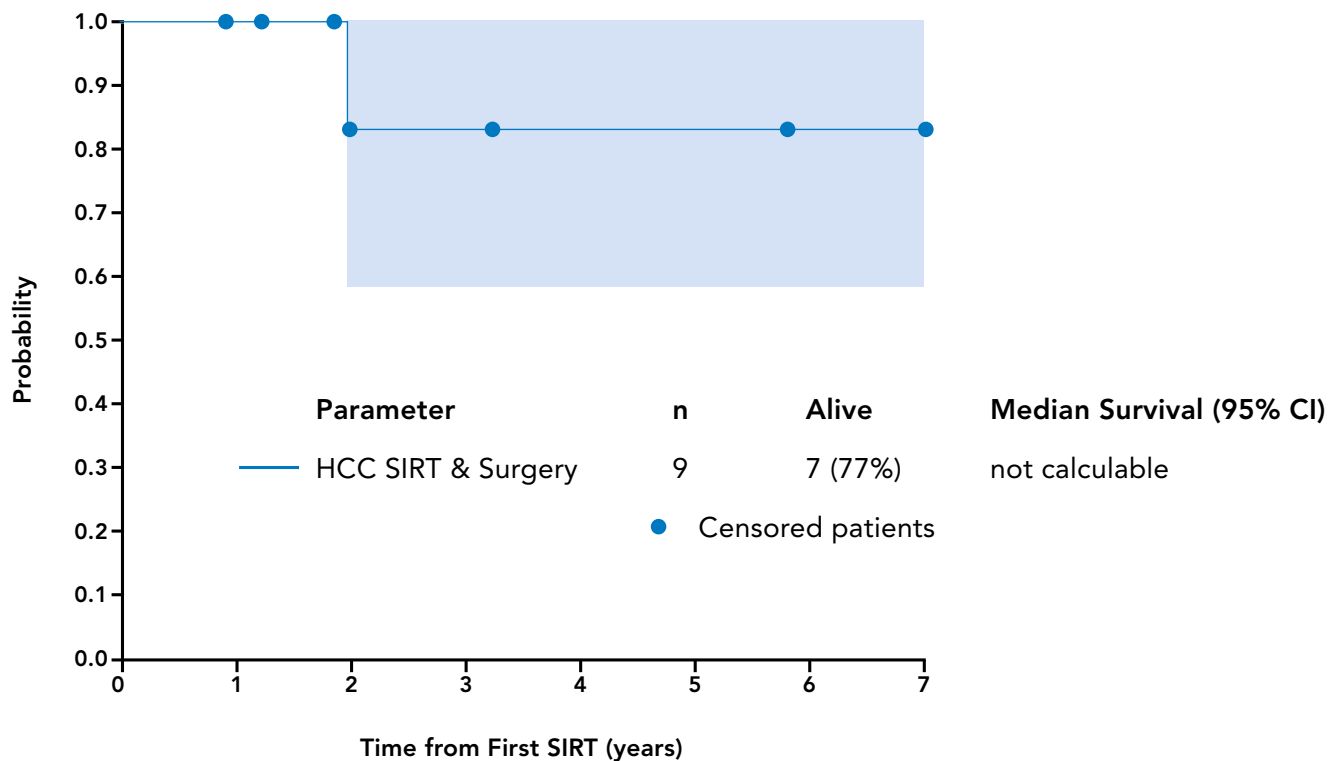
Some of these intermediate and advanced stage HCC have responded so well to SIRT therapy that they have been down-staged and have become eligible for ablative therapy such as surgical resection, radio-frequency ablation and liver transplantation.

## SURGICAL RESECTION FOLLOWING DOWN-STAGING WITH SIRT AT NCCS

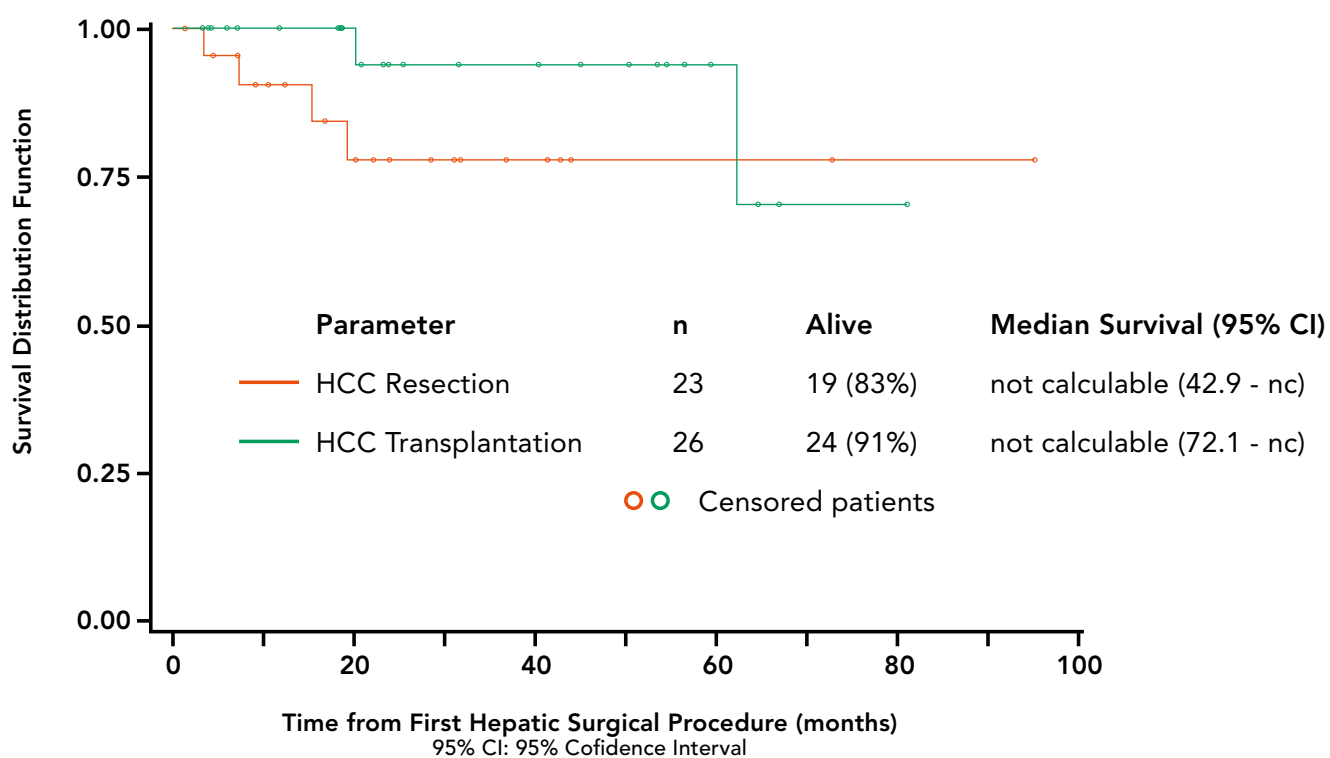
A total of 9 patients managed by NCCS have undergone surgical resection following down-staging of HCC from TNM stage III or II to stage I. Surgical resection was carried out at a median of 7.2 months after initial treatment with SIRT. Surgical resection was found to be safe in such patients with no major post-surgical complications.

Excellent overall survival outcomes were found. At an average follow-up of 34.2 months, median survival has not been reached (see Graph 1).

**Graph 1** Survival from SIRT and surgery for HCC (NCCS Data)



**Graph 2** Survival from surgery for HCC (international data from the P4S study – with permission)





### INTERNATIONAL EXPERIENCE WITH DOWN-STAGING OF HCC TO RESECTION WITH SIRT

An international consortium of 13 centres (including NCCS) have pooled their experience of surgical resection and transplantation following down-staging of 51 cases of HCC with SIRT. This was part of a larger study that looks at liver resection and transplantation following SIRT for a number of different cancers [***Retro-spective Post SIR-Spheres Surgery in Previously Unresectable Hepatic Malignancy Study (P4S)***].

In this international study, at a median follow-up of 38.3 months after SIRT, median survival has also not been reached (*Graph 2*). The results are consistent with the NCCS experience.

### FURTHER STUDIES

These clinical outcomes, while encouraging, must be confirmed by a formal prospective clinical trial. All the patients in the above studies were initially un-resectable and subsequent surgical resection was fortitious.

Of greater interest in the context of a clinical trial would be to study if outcomes in intermediate-stage patients can be improved by neo-adjuvant down-staging. Planning for a prospective study for this indication has commenced.



*Professor Pierce Chow* is an academic surgeon and Professor at the Duke-NUS Medical School. He is concurrently Senior Consultant Surgeon at the National Cancer Centre Singapore (NCCS) and the Singapore General Hospital (SGH), and NMRC Senior Clinician Scientist. Prof Chow's interests are in oncology and the development of medical devices.

He has successfully led multidisciplinary teams in translational oncology research and has been protocol chair of multinational investigator-initiated clinical trials. He was conferred the 2012 NMRC National Outstanding Clinician Scientist Award for his research on liver cancer.



GPs can call for appointments through the GP Appointment Hotline at 6436 8288 or scan the QR code for more information.

# The Art of Precision – Modern External Beam Radiotherapy



Dr Looi Wen Shen, Registrar,  
Division of Radiation Oncology, National Cancer Centre Singapore

Radiation therapy, together with surgery and chemotherapy, is one of the three pillars of modern cancer therapy. Radiation therapy involves the use of ionising radiation to kill cancer cells through free radical formation and DNA strand breaks. Since the discovery of X-rays by Wilhem Röntgen in 1896, radiotherapy has evolved from a crude remedy into a precise art, requiring collaboration across a team of doctors, physicists, dosimetrists and radiation therapists to accurately target cancer tissues.

This improved precision has allowed higher doses of radiation to be delivered to tumours, resulting in improved chances of cure and control, whilst sparing more normal tissues and reducing potential toxicities.

Radiation therapy can either be delivered externally (external beam therapy) usually with linear accelerators or internally (brachytherapy) through the use of radioactive elements placed close to the tumour. The most common modalities are photons and electrons, although particle therapy such as proton and ion therapy is becoming more common. Due to the breadth of this topic, this article will focus on the advanced techniques of external beam radiotherapy with photons only.

## TREATMENT PLANNING

“If you fail to plan, you are planning to fail!” This quote by Benjamin Franklin is profoundly apt for radiotherapy. Successful treatment planning with radiation therapy requires careful collaboration between all members of the team and due to the complexity of modern techniques, the entire process may take several days to complete.

1. Treatment planning begins with a procedure known as **simulation**. It involves positioning the patient in a position which is comfortable enough to maintain for at least 15 minutes, and yet suitable for the optimal delivery of radiotherapy.
2. **Immobilising the patient** through the use of various devices and making tattoos for position reference follows this. If the positioning of the patient is complex, photos may be taken to aid with reproducibility of setup position at the treatment unit.
3. A **CT simulation** is then performed. For treatment at certain sites such as the lung, 4-dimensional CT imaging may be required. This is so-called because it takes into account motion with time. By acquiring a large number of images over time, the movement of the tumour, e.g. through different phases of respiration, can be viewed. The scanned images are then imported into the treatment planning system software.
4. Defining the region to be irradiated, known as **target delineation**, ensues. Technology has blessed us with ever-improving imaging with higher resolution, allowing greater discernment of tumours. Co-registration of MRI and PET imaging with CT simulation images affords us even more information with which to base target delineation.
5. Combining this with the clinical and pathological information, the clinician then gives **additional margins** for potential microscopic involvement and uncertainties in position, planning and delivery when deciding the final planning target volume (PTV). This ensures that radiotherapy is delivered as intended to the tumour.



The dosimetrists and physicists use complex computer software modelling, allowing estimations of the radiation dose to the target volume and the normal structures. By varying parameters such as gantry angles and shielding, among others, an individualised plan for the patient can be created.

The total amount of radiation (measured in units called Grays) delivered will be prescribed. This is often divided into smaller doses known as fractions and given over several days or weeks. In certain circumstances the total radiation dose may be given in a single fraction.

All this data is then exported to the treatment machines for delivery of radiation to the patients.



Figure 1 CT Simulator

### TREATMENT DELIVERY

In the early days of radiotherapy, delivery was limited to simple rectangular fields with limited shielding of normal structures. As a result, it was difficult to protect vital structures, resulting in potentially devastating long-term side effects when higher doses were required. By amalgamating our improved understanding of biology and physics, the digital era has ushered new techniques for us to tip the scales in favour of our patients.

The more advanced external beam therapy techniques include **1.** Intensity Modulated Radiotherapy (IMRT), **2.** Volumetric Modulated Arc Therapy (VMAT), **3.** Tomotherapy®, **4.** Image Guided Radiotherapy (IGRT), **5.** Stereotactic Radiotherapy (SRT), **6.** Adaptive Therapy and **7.** 4-Dimensional Radiotherapy.

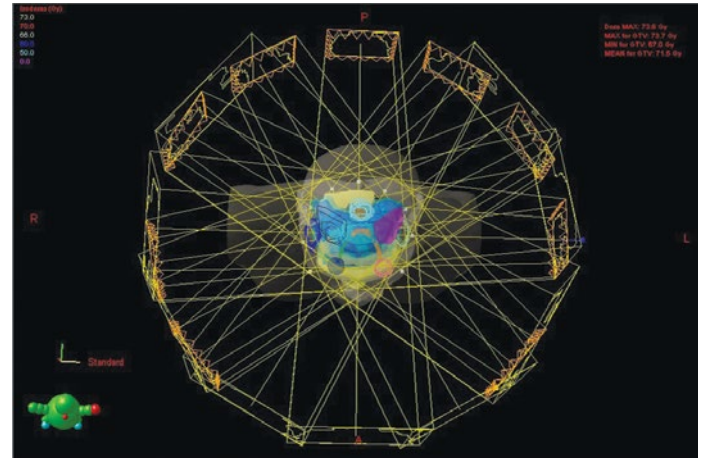


Figure 2 Intensity modulated radiotherapy (IMRT) planning

#### 1. Intensity modulated radiotherapy (IMRT)

IMRT allows shaping of the dose distribution around the tumour. This is done by delivering the radiation from different angles and the use of multileaf collimators (MLC). MLCs are miniature strips of shields that block radiation in the portal. These work together to create complex radiation fields. These MLCs may remain static (static IMRT) or move (dynamic IMRT) during the delivery of radiation.

**IMRT has greatly advanced the treatment of head and neck cancers by allowing dose escalation with fewer severe side effects such as mucositis and xerostomia.**

#### 2. Volumetric Modulated Arc Therapy (VMAT)

VMAT technology builds further on IMRT technology. Radiation is delivered while the gantry rotates. This allows adjustment of different variables such as gantry rotation speed, dose rate and MLC position while the beam is moving. Not only can complex dose distributions be achieved, but treatment time is significantly shorter.

**This treatment is especially suitable for patients who are unable to remain in the treatment position for prolonged periods of time, but yet require conformal dose distributions, e.g. patients with significant pain.**



Figure 3 Volumetric Modulated Arc Therapy – RapidArc® by Varian Medical Systems

### 3. Tomotherapy

In tomotherapy, radiation is delivered much in the same way a CT scanner scans a patient. The treatment couch moves through a doughnut-shaped gantry while the radiation is delivered. Within the gantry, the linear accelerator is able to move around and target the tumour from all angles. The radiation dose is thus delivered in a helix as the patient moves through the gantry.

Together with mini MLC, complex dose distributions can be delivered to large volumes, since a large portion of the patient can be moved through the gantry during delivery. Tomotherapy is often used for many different treatment sites due to the excellent dose distribution that can be achieved.

**One group of patients that benefits especially from tomotherapy is those requiring cranio-spinal irradiation (CSI) for tumours such as medulloblastoma or CNS germinoma.**

In the past, CSI required multiple fields with complicated matching of fields, which was time-consuming for both patient and staff.

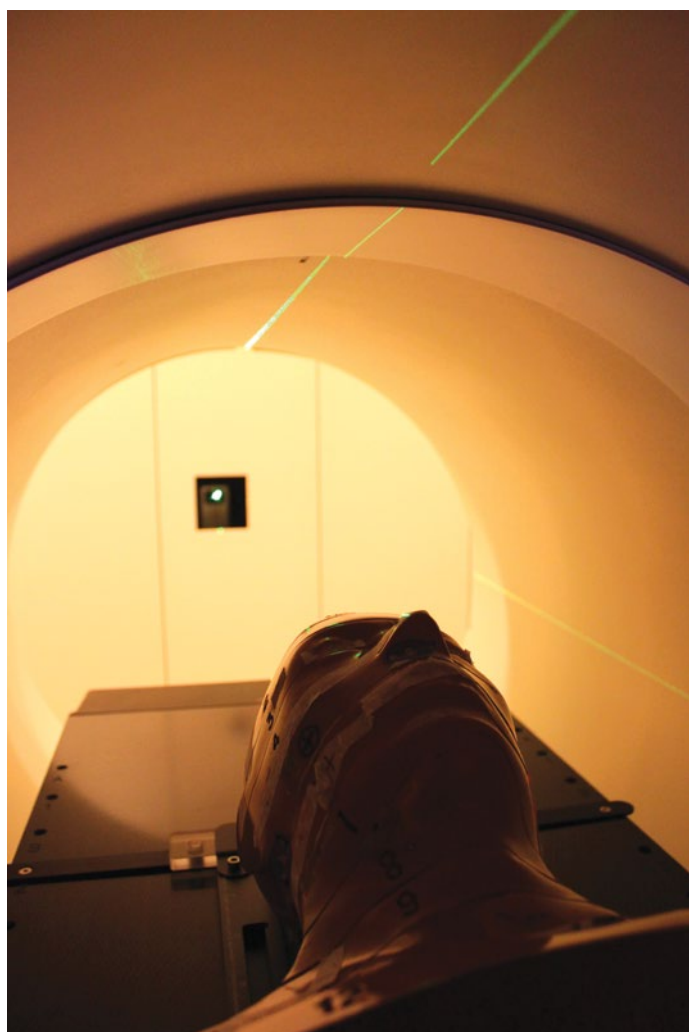


Figure 4 Head and neck phantom in Tomotherapy machine

Using tomotherapy, the whole cranio-spinal axis can be treated together as one field since the whole area can be moved through the treatment gantry together. Additionally, they benefit from the steep dose gradients that can be achieved.

### 4. Image Guided Radiotherapy (IGRT)

Image guided radiotherapy refers to the use of frequent imaging during the course of radiation therapy to verify accurate treatment delivery. A scanner is mounted on the treatment machine, allowing images of the treated area to be viewed just before the dose is delivered. This allows verification that the radiation dose is reaching the intended target volume.

By using IGRT, tighter margins can potentially be given when generating the PTV (as mentioned previously under treatment planning). The result is that less radiation is ultimately given to normal tissue around the tumour with potentially fewer side effects.

**Patients being treated at sites that may move significantly, e.g. prostate and bladder, benefit from this technique.**

### 5. Stereotactic Radiotherapy (SRT)

Stereotactic radiotherapy is so-called because it enables extremely precise delivery of radiotherapy to ablate tumours. High doses are given in a small number of fractions to treat small volumes, whilst keeping normal tissue dose to a minimum.

This is achieved through tightly-collimated radiation beams with sharp dose fall-off at the edges together with precise patient positioning. Additionally, certain treatment systems allow delivery of radiation through angles on more than one plane (non-coplanar treatment).

Stereotactic radiotherapy is frequently employed in the treatment of early stage non-small cell lung cancers not suitable for surgery. **It is particularly useful for solitary or oligometastatic disease, especially in the brain and spine. By focusing the beams onto the tumour with high doses in few fractions, ablation of the tumour is possible.**



Figure 5 Stereotactic Radiotherapy with Novalis system



### 6. Adaptive Radiotherapy

Adaptive radiotherapy is at the forefront of advanced radiation therapy. During the course of radiation treatment, the anatomy of the patient and tumour may change, for example due to weight loss or tumour shrinkage. Thus, the planned dose distribution of radiation may not match what is being delivered.

Adaptive radiotherapy involves changing, i.e. adapting the radiotherapy plan after treatment has already started and can occur at different time frames. The different time frames are: 'offline' between fractions; 'online' just prior to delivery; and 'real time' during a treatment.

**The head and neck is a region that particularly benefits from adaptive radiotherapy.** Large neck nodes can shrink significantly during the course of radiotherapy, creating a discordance between planned radiotherapy delivery and what is actually delivered. By adopting adaptive radiotherapy, this can be reduced.

### 7. 4-Dimensional Radiotherapy

4D radiotherapy involves three-dimensional delivery of radiotherapy, taking into account the 4th dimension of time. As mentioned earlier, tumours may move in the body, for example in the lung during the respiratory cycle.

By monitoring the movement pattern through tracking devices, it is possible to turn the beam on only when the tumour is in the desired portion of the respiratory cycle. This is known as gating. Certain systems employ fiducials or even electromagnetic transponders implanted into the target tissue to allow tracking of the tumour real-time.

**4D radiotherapy has a big role in lung cancer treatment. The large motion produced by the diaphragm, especially for lower lobe tumours requires bigger margins and hence bigger target volumes for treatment. This can be abrogated to an extent by the use of 4D radiotherapy.**

### THE FUTURE – PROTON THERAPY?

Protons are positively-charged subatomic particles that can produce favourable dose distributions. They are produced by machines called cyclotrons and synchrotrons and are then energised to specific velocities, depending on the intended depth of penetration.

As protons travel through the patient, energy is transferred, which results in ionisation. However, most of the energy is transferred right at the end of the path, resulting in a very localised deposition of dose. This opens the door to better dose distribution with more dose to the planned target volume and less to the normal tissues.

**One group of patients that benefits greatly from proton therapy is children. The last few decades have seen the overall survival rate in childhood cancers increase from 10% to almost 90%. Since these patients are surviving longer, being afflicted with late side effects is even more detrimental.**

### CONCLUSION

Radiotherapy continues to evolve since its inception. Technological improvements in imaging and radiation delivery over the last few decades have allowed more precise delivery of radiotherapy in more complex dose distributions.

This has allowed higher doses to be achieved within tumours whilst sparing normal tissues. The increased complexity of treatment requires careful planning and collaboration between all members of the treatment centre.



Dr Looi Wen Shen is currently a Registrar in the Division of Radiation Oncology of National Cancer Centre Singapore. His main clinical and research interests lie in the field of paediatric radiation oncology.



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# “Catching Cancer”

## – Head & Neck Cancer and Multidisciplinary Care

■ Assoc Prof N Gopalakrishna Iyer, Head, SingHealth Duke-NUS Head & Neck Centre;  
Senior Consultant, Division of Surgical Oncology, National Cancer Centre Singapore

Dr Mahalakshmi Rangabashyam, Service Registrar,  
Division of Surgical Oncology, National Cancer Centre Singapore

Amongst all the cancers, head and neck cancers (HNC) are probably one of the most challenging cancers to treat and the most distressing to patients since as a site, the head and neck comprises the most intricate anatomy and governs critical physiologic functions.

The areas of functional responsibility encompassed within this dense region are vision, hearing, balance, olfaction, taste, swallowing, voice, endocrine, proximity to central nervous system and most importantly, facial expressions.

Though on the surface they are seemingly closely-connected, they are most diverse and heterogeneous in terms of tumour biology, behaviour, function and outcome.

Treatment goals are balanced between cure, improved survival outcomes, and ability to tolerate treatment (due to comorbid illness), and of paramount importance is the preservation of organ function if possible. Needless to say, the possible disfigurement (cosmetic outcome) with the attended psycho-social impact of a visualised scar just adds to the overall complexity of treatment planning.

Epidemiological data suggests that the incidence of HNC constitutes for 12% of all malignancies in the world, and is the fifth most common cancer type and cause for cancer-related deaths worldwide.

According to the Singapore Cancer Registry, the most common head and neck cancer is nasopharyngeal carcinoma (NPC), which features as the eighth most common cancer amongst Singaporeans.<sup>1</sup>

### AETIOLOGY

Squamous cell carcinomas (SCC) of the upper aero-digestive tract predominate and are related to **tobacco (cigarettes and smokeless tobacco) and alcohol consumption**. Other histological forms are salivary gland tumours, skin cancers and sarcomas.

Established viral infections postulated to play a role in carcinogenesis are **Epstein Barr Virus (EBV)** in NPC, and increasingly evident is the association between **Human Papilloma Virus (HPV)** and **oropharyngeal carcinoma** (which is linked to sexual practices). HPV-positive cancer patients tend to be in contrast to the typical HNC patient – they are young, non-smokers and probably non-drinkers. Patients who are positive for HPV usually carry a better prognosis.<sup>2</sup>

Additional aetiological factors include **chronic trauma** from sharp teeth and ill-fitting dentures for oral cavity SCC.

**Past medical history of head and neck radiation therapy (RT)** is important to note and is a potential risk factor for second primary, relevant in Singapore for patients treated for NPC many decades ago.<sup>3,4</sup>

**‘Field cancerisation’** occurs due to the wide area of exposure to tobacco and alcohol, and can predispose to second primary as well.

Monitoring **pre-malignant conditions** like lichen planus, submucosal fibrosis, leukoplakia and erythroplakia is crucial.

**Family history** plays a role in the detection of thyroid cancers and NPC. Research indicates that genetic components and mutations specific to Asians can impact prognosis of tongue SCC, and provides invaluable information for future targeted therapy.<sup>5,6</sup>

*“If you don’t do the operation the tumor will!!!”*

*- John Joseph Conley (1912-1999)*

*A musician, poet, painter and incidentally a head and neck surgeon. He is the first President of the American Society for Head and Neck Surgery in 1959.*



### Head and Neck Cancers and Common Symptoms

Sub-site	Symptoms
Nasal cavity and paranasal sinuses	Blocked nose, reduced smell, nasal discharge, epiphora, visual disturbances
Oral cavity	Trismus, hot potato voice, impaired tongue mobility
Nasopharynx	Neck lump, ear block, unilateral tinnitus, nose block
Oropharynx	Neck lump, dysphagia and odynophagia, chronic cough
Larynx	Hoarseness, choking/aspiration, stridor, cough, and globus sensation
Hypopharynx	Dysphagia, odynophagia, aspiration, neck lump
Metastatic neck (unknown primary)	Neck lump
Thyroid	Visible hard neck lump or incidental finding radiologically
Temporal bone	Ear pain, muco-pus discharge and impaired hearing
Skin	Chronic ulcer, pigmented lesion, altered sensation

Note: Common symptoms for all sub-sites are bleeding and blood-stained secretions/discharge.

#### EXAMINATION

The complete head and neck evaluation entails detailed history-taking with special attention to personal history (exposure of risk factors), general examination, and thorough local examination.

At times, specialists are so focused on scoping the dysphonic, dysphagic patient that examination of the oral cavity is cursory and lesions afflicting the soft palate, floor of mouth, and ventral tongue can be potentially missed!

**A high degree of suspicion is essential since HNCs are notorious for masquerading under the blanket of benign symptoms.**

Common clinical scenarios:

- a. Non-healing oral ulcer – Oral cavity Ca.
- b. A young patient with asymmetric tonsils – Tonsillar Ca.
- c. Blocked ear unilateral tinnitus, and/or neck lump – NPC.
- d. Chronic cough and hoarseness in a smoker – Laryngeal Ca.
- e. Recurrent aspiration pneumonia – Hypopharyngeal Ca.

- f. Globus-like symptoms in an anaemic lady – Post cricoid Ca.
- g. Chronic skin lesion ulcer or pigmented lesion – sun-exposed area – basal cell carcinoma (BCC), SCC, or malignant melanoma.
- h. Unexplained blood-stained discharge – ear, nose, oral cavity and pharynx – common denominator for most HNCs.

Patients are likely to present to the local GP during the first symptom, possibly during the initial stages. Early referral and intervention by the specialist is critical and can save the patient from locally advanced disease and possibly distant metastasis.

#### Early Identification

Recent advances suggest that given the propensity for NPC to metastasise and consequently poorer prognosis, early identification of aggressive NPC with biomarkers can be treated more aggressively.<sup>7</sup>



Erythroplakia buccal mucosa



Ventro-lateral surface tongue SCC



Soft palate tumour

It is good practice to emphasise early follow-up visits when lesions persist. Assiduous work-up is indicated for all suspicious lesions. It is unacceptable to delay diagnosis further on account of prolonged follow-up visits to review ordered results.

### Investigation

Investigations usually include local excisional or incisional biopsy, fine-needle aspiration cytology (FNAC) of the neck lump, MRI/CT-scanning of the primary site and CT chest abdomen and pelvis, and PET scans for staging and pre-treatment planning.

### MANAGEMENT

As the disease progresses, management goals can swing from attempted cure to palliation. Decisions are collectively taken by a multidisciplinary team at Tumour Board Meetings. The importance of early referral warrants reiteration. The histology type, site, depth of invasion (adjacent bone or soft tissues), lymph node involvement (LN), stage, presence of previous treatment in the form of RT/surgery and anticipated response to treatment will dictate the choice of treatment to the primary site and neck if involved.

### Early Stages I and II

Typically, early stages I and II usually employ single modality treatment [surgery, chemo-radiation therapy (CRT) or RT], as opposed to advanced stage requiring multimodality management. In the event that there is failure post-RT, salvage option could possibly be through surgery. Post-surgery impaired wound healing is not uncommon and can be recalcitrant; and vacuum assisted closed drain system is leading to improved outcomes.<sup>8</sup>

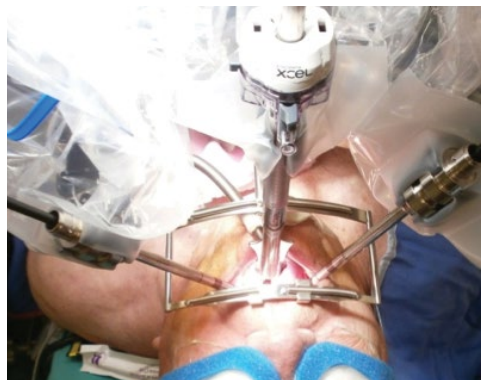
The treatment truly begins at surgery and doesn't usually end with it. The HN surgeon plays a pivotal role at every step, during initial evaluation, diagnosis, treatment planning, and last but not least, management of relapse or recurrence.

### Minimally Invasive Surgery

Noteworthy to mention is the evolution of minimally invasive surgery in the form of Transoral Robotic Surgery (TORS), specifically for resections of oropharyngeal neoplasms and selective supraglottic lesions as a favoured option over CRT.<sup>9, 10</sup>

Improved outcomes are possible because of reliable oncological resection enabled by wristed instruments and superior endoscopic magnified visualisation. This eliminates the need for an external incision which results in reduction in morbidity, recovery time, and hospital stay.

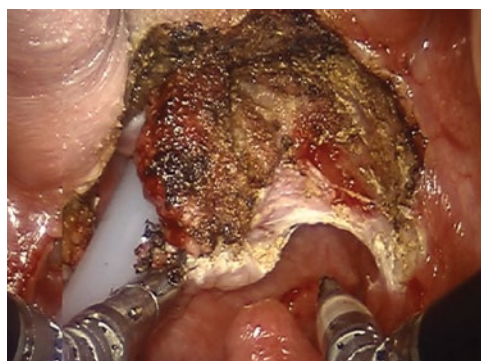
The downside is the economic affordability. The service of robotic surgery for HNCs is available through the SingHealth Duke-NUS Head and Neck Centre at the Singapore General Hospital (SGH).



Transoral robotic surgery



Left tonsillar SCC



Radical tonsillectomy

### Multidisciplinary Care

In the evolution of HNC management, a salient landmark is multidisciplinary teamwork (MDT). The head and neck surgical-oncological team, reconstructive team, radiologists, pathologists, radiation and medical oncologists, palliative team, and finally the allied health team (dietitian, speech therapists, psychologist, physiotherapist) have collectively formed a plexus to render customised cancer care service specific to every patient.

The different specialists may have differing opinions, but are united by a common outlook and a desire to work in the best interest of the patients and improve quality of life.



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*Assoc Prof N Gopalakrishna Iyer* heads the SingHealth Duke-NUS Head & Neck Centre, and is a head and neck surgeon in National Cancer Centre Singapore and Singapore General Hospital. He has extensive experience in the surgical management of head and neck cancers, as well as surgery for benign diseases in the head and neck (including thyroid, salivary gland and skin lesions).

He is actively involved in research and leads a number of research programmes that aim to determine prognostic factors in oral cancers, identifying the cause of head and neck cancers in young people and development of novel therapeutic strategies in treating these cancers.



*Dr Mahalakshmi Rangabashyam S* is a Service Registrar in the SingHealth Duke-NUS Head & Neck Centre, and the Division of Surgical Oncology at the National Cancer Centre Singapore. She did her post-graduate training in Otolaryngology in India. Her area of interests are in sleep, otology and head and neck cancer.

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# Corneal Transplantation: From PK to LK – A Paradigm Shift

Dr Arundhati Anshu, Senior Consultant,

Department of Cornea and Refractive Surgery and Department of General Cataract and Comprehensive Ophthalmology, Singapore National Eye Centre

As the protective window that controls the entry of light into the eye, the cornea plays an important role in enabling us to see.

But should things go wrong, the Singapore National Eye Centre's (SNEC) team of corneal ophthalmologists are well-versed in providing medical and surgical care to treat patients with corneal disorders.

We take care of patients who need:

- 1) Corneal transplantation
- 2) Contact lens-related eye problems
- 3) Infectious keratitis (corneal ulcers)
- 4) Ocular surface disorders requiring reconstruction
- 5) Treatment for dry eye
- 6) Artificial corneal transplant

The Singapore Corneal Transplant Programme was initiated in 1991 and since then, SNEC has been performing over 350 corneal transplants a year, with an overall graft survival rate exceeding 90%. Nearly 3,500 transplants have been performed to-date.

## WHO WOULD BENEFIT FROM A CORNEAL TRANSPLANT?

Individuals with poor vision due to a diseased or cloudy cornea, with healthy optic nerve and retina, may benefit from a corneal transplant to see well.

Whenever vision is reduced from corneal disorders like infections, corneal injuries/scars and degenerative diseases, a corneal transplant can be an effective means of restoring vision.

## HOW IS A CORNEAL TRANSPLANT PERFORMED?

There are several types of corneal transplant procedures that are performed in SNEC. Broadly, these include 1) full-thickness corneal transplants or penetrating keratoplasty (PK), 2) partial thickness corneal transplants or lamellar keratoplasty (LK) [viz: anterior lamellar keratoplasty (ALK)], and 3) endothelial keratoplasty (EK) (Figure 1).

### 1. Penetrating keratoplasty (PK)

PK is a form of microsurgery in which the central 7-8 mm portion of the diseased cornea is removed and replaced with a clear and healthy donor cornea. The donor cornea is held in place with very fine microsurgical nylon sutures.

### 2. Lamellar keratoplasty (LK)

In LK, only diseased corneal layers are replaced, preserving healthy corneal tissue. When only the anterior layers (corneal stroma) of the cornea are replaced, the procedure is called anterior lamellar keratoplasty (ALK).

#### Deep anterior lamellar keratoplasty (DALK)

DALK is one such form of ALK in which most of the anterior layers of the cornea are removed sparing the posterior corneal layer [Descemet membrane (DM) and endothelium].

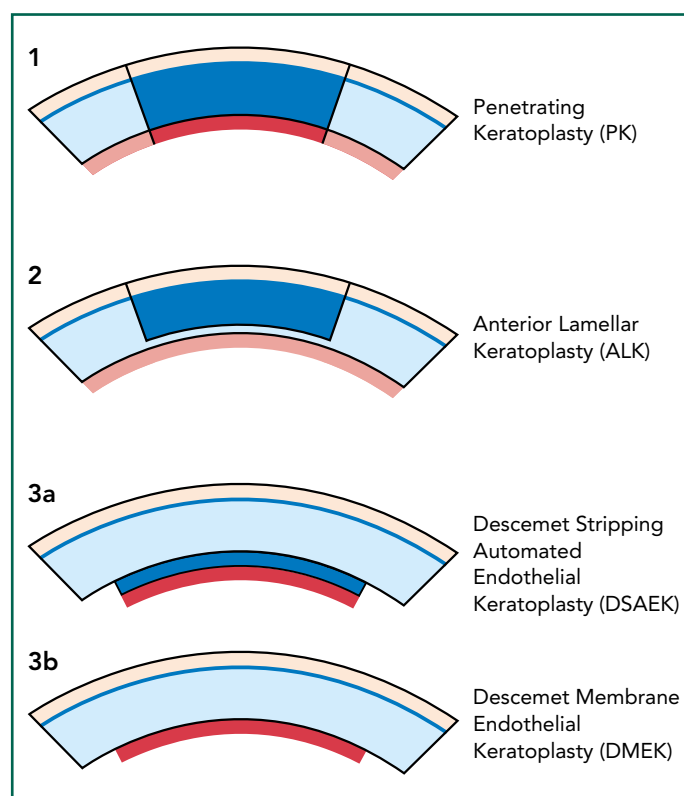


Figure 1 Different types of corneal transplant procedures



About 40% of corneal transplants at SNEC are performed with DALK procedures. SNEC today is one of the few transplant centres in the world that offers these new and advanced techniques of LK to our corneal patients.

SNEC is the regional centre in Asia for DSAEK surgery and more than 40% of transplants in SNEC are DSAEKs. DSAEK is probably the most significant advance in the field of corneal transplants.

### 3. Endothelial keratoplasty (EK)

When only the diseased posterior layers of the cornea (DM and endothelium) are replaced, the procedure is called endothelial keratoplasty (EK).

EK today includes:

- a) **DSAEK – Descemet Stripping Automated Endothelial Keratoplasty**
- b) **DMEK – Descemet Membrane Endothelial Keratoplasty.**

#### a) **DSAEK**

In DSAEK, only the inner layer of the donor cornea, about a 10th of a millimeter thick, is transplanted onto the patient's own cornea through a small 4-5 mm incision at the side of the cornea.

#### **The Tan EndoGlide**

SNEC and SERI's team of scientists have been working on continually improving the technique of DSAEK and were the first to pioneer a surgical device, the Tan EndoGlide, in 2009, to perform DSAEK. Licensed to a UK surgical company, the EndoGlide is the first FDA-approved device for DSAEK.

This device enables donor insertion into the patient's eye with ease and minimises donor trauma that can occur while inserting into the eye through a small incision.

It has been the most successful surgical device to implant this donor tissue through a keyhole incision. It has the best published safety record compared to other devices, and over 5,000 corneal transplants using this device have been performed around the world to-date.

The Tan Endoglide was first used in 2009 as part of the SNEC DSAEK EndoGlide Clinical Trial. We have reported our results using this device and have achieved very good visual outcomes and lower rates of endothelial cell loss as well as reduced risks of complications (Khor WB et al).<sup>1</sup> Similar good outcomes have also been reported from another centre that has successfully adapted this device for DSAEK surgery (Hollick E et al).<sup>2</sup>

#### **b) DMEK**

DMEK is the latest innovation in the form of minimally invasive, sutureless, corneal transplant surgery. Instead of implanting a 10th mm thick donor in DSAEK, this new complex procedure now just replaces the actual damaged corneal endothelial cell layer which is just 1/100th mm thick.

In selected patients, this has the advantage over DSAEK in that patients have the possibility of attaining 6/6 vision within a few weeks after surgery. Additionally, it may be associated with a lowered risk of rejection as suggested by a recently published article (Anshu et al).<sup>3</sup>

Currently however, DMEK is suitable for milder forms of corneal oedema and may not be suitable for all patients.

#### **WHERE DOES THE DONOR CORNEA COME FROM?**

All corneas transplanted at our Centre are of excellent quality and procured by the Singapore Eye Bank (SEB). SEB gets corneas from local donors in Singapore, as well as from internationally accredited eye banks in the United States of America and other international eye banks around the world.

Because the SEB is very successful in procuring corneal tissue, one usually has to wait only a couple of weeks to receive a donor cornea. SEB also provides corneas for non-Singaporeans undergoing corneal transplants in Singapore. Singapore is a leading transplantation Centre in Asia, with many international patients successfully undergoing transplantation surgery here.

#### **WHAT ARE OUR OUTCOMES WITH THESE CORNEAL TRANSPLANT PROCEDURES?**

The success rate for uncomplicated corneal transplants is about 91% in the first year. However, complications can occur following a transplant. The more common complications that can occur include raised intra-ocular pressure, which can cause damage to the optic nerve (glaucoma), and corneal graft rejection.

Most of the complications occur in the first year after transplantation, but most can be treated successfully if detected early.

There are very few countries that have long-term follow-up, and our Singapore Corneal Transplant Study (SCTS), which spans more than 20 years, is one of the largest transplant databases worldwide.

Our results in Singapore show that the results in Asian eyes in our Centre are equivalent to that of Caucasian eyes in the West, and ours is the only major database monitoring success in Asian eyes.

### Anterior Lamellar Keratoplasty (ALK)

Nearly 40% of corneal transplants in SNEC are LKs. Because ALK retains the innermost corneal layer, it greatly reduces the risk of corneal graft rejection, a significant cause of corneal transplant failure.

Compared with the 20% overall risk of rejection after PK, rejection risk following ALK is less than 1%.<sup>4</sup> There is also better long-term graft survival following ALK. Our SCTS results show that the overall 1-year graft survival for ALK in SNEC is 94%.

In terms of recovery of vision, we have been able to achieve equal if not better visual outcomes following ALK as compared with PK performed for similar indications.<sup>5</sup>

### Endothelial Keratoplasty (EK)

In SNEC, more than 100 cases of EK are performed yearly, and SNEC leads the field in EK surgery in Asia. EK offers several advantages over a full-thickness procedure like PK in patients with selective damage to the inner layers of the cornea (endothelium):

1. **No suture-related problems:** Because EK does not involve any donor suturing onto the patient's cornea, it does not have the risk of suture-related problems like suture-related abscess. There is also reduced astigmatism, resulting in better vision when compared with PK.
2. **Lower risk of graft rejection:** Early results have shown that the risk of rejection is much lower with EK. Compared with the 20% overall risk of rejection after PK, rejection risk following EK is just 7.6% in the first year.<sup>5</sup>
3. **Very good graft survival:** Graft survival appears to be excellent in our SNEC series, with very few failures occurring to date. Graft survival appears to be better than conventional PK surgery. This may be related to the lower risk of graft rejection.
4. **Faster visual recovery:** The visual recovery is much faster following an EK procedure with reduced astigmatism compared with PK.

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~~Dr Arundhati Anshu is a Senior Consultant in the Departments of Cornea and Refractive Surgery as well as General Cataract and Comprehensive Ophthalmology of the Singapore National Eye Centre (SNEC).~~

~~She is also the Associate Program Director of fellowships in SNEC and Adjunct Assistant Professor in the NUS Yong Loo Lin School of Medicine (NUS YLLSoM) as well as Duke NUS Medical School, Singapore. She has been actively involved in research and teaching for over a decade.~~



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# The Heart of the Matter

## Singapore heart patients' main concern is end-of-life care

Getting appropriate treatment and prolonging life span may not always be the goals of patients with chronic conditions.

To heart failure patients in Singapore, as one study revealed, it was the challenge of planning for end-of-life care arising from the uncertainty in prognosis. The study was published in Proceedings of Singapore Healthcare recently.

### CARE ISSUES

While physical and psychological concerns were also there, many patients spoken to during focus group sessions highlighted end-of-life care issues, particularly in wanting to avoid undue prolongation of their life. They were worried about being a burden to their family members by requiring extensive care, spending family resources, or causing emotional distress.

"As a result, patients often based care decisions on what they believed would be best for their family," said lead author of the study, Assistant Professor Chetna Malhotra, Lien Centre for Palliative Care, Programme in Health Services and Systems Research, Duke-NUS Medical School.

**Healthcare providers can help allay these fears by not only discussing treatment plans with patients and their family members but also by initiating Advanced Care Planning conversations.**

### NAVIGATING THE HEALTHCARE SYSTEM

Navigating the healthcare system proved to be a challenge for these patients too, according to the study. As many of them were elderly with multiple comorbidities, they faced difficulty in juggling instructions and multiple medications, as well as in deciding which advice or treatment plan to prioritise.

**"Instead of visiting multiple physicians, it may be less complicated for them to consult one physician who is aware of all their conditions and is able to advise them holistically.**

The physician can be backed by tertiary healthcare support should the need arise," said Asst Prof Malhotra.

### PRIMARY CARE

**Primary care physicians are probably best-placed to manage these patient concerns especially if the patients are regulars at their clinics.**

"Heart failure however can be a challenge to manage as it is a rapidly developing field," said study co-author Adjunct Assistant Professor David Sim, Senior Consultant, Department of Cardiology, National Heart Centre Singapore.

There are several useful clinical guidelines such as the ones provided by American Heart Association, European Society of Cardiology and Ministry of Health, Singapore.

**"These guidelines are very comprehensive. Primary care physicians just need to keep in mind that heart failure is a chronic disease which needs a multidisciplinary approach, and keep up-to-date with the latest information," he added.**







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Academia, Singapore General Hospital  
20 College Road, Level 1, Singapore 169856

**Call For Abstract** Deadline: 15 July 2016

Participants are invited to submit abstracts for oral/poster presentations on any aspect of stroke. All abstracts must be submitted electronically together with the Registration Form. Abstract Submission Form can be downloaded from [www.nni.com.sg/Education/documents/16ssc.html](http://www.nni.com.sg/Education/documents/16ssc.html)

CONFERENCE REGISTRATION FEES			
Registration Category	Early Registration Registration and payment must be made before 31 July 2016	Normal Registration Registration and payment must be made before 16 September 2016	On-site Registration All registration and payment received after 16 September 2016 will be considered as on-site registration.
<b>a) Main Conference (7 October – 8 October 2016)</b>			
<sup>1</sup> Physicians and Researchers	\$S150.00	\$S200.00	\$S250.00
<sup>2</sup> Trainees, Nurses, Allied Health Professionals and other Medical Professionals	\$S100.00	\$S150.00	\$S200.00
<small>Note: *All prices quoted are in Singapore Dollars (SGD) and are inclusive of prevailing taxes. *This symposium is for healthcare professionals only. **Associate Consultants, Consultants and Senior Consultants are considered as Physicians. Others will be considered as Trainee. **Trainee/Student identification or proof of qualifying trainee/student status MUST accompany the registration form to qualify for Trainee/Student fees. Proof of status is also required when registering on-site.</small>			
<b>b) Pre-Conference Workshop (6 October 2016)</b>			
<b>Stroke Nursing Workshop: Integration of Science &amp; Art</b> (Limited Seats Available, AM Session)	<b>Stroke Thrombolysis Simulation Workshop</b> (Limited Seats Available, PM Session)		
	\$S50.00		\$S100.00



## Courses

# GP Forum 13<sup>th</sup> Practice Update in Paediatrics

Time	Programme
1.00 pm	Lunch reception and Registration
2.00 pm	<b>Advances in Management of Paediatric Brain Tumours</b> <i>Adj Asst Prof David Low, Head and Consultant, Neurological Service, KKH</i>
2.40 pm	<b>What a Pain! Headache and Chronic Pain Management in Children</b> <i>Dr Angela Yeo, Consultant, Dept of Anaesthesia (Paediatrics), KKH</i>
3.20 pm	Tea refreshment
3.40 pm	<b>Updates in Management of Paediatric Respiratory Conditions</b> <i>Dr Teoh Oon Hoe, Deputy Head, Dept of Paediatrics, Head and Senior Consultant, Respiratory Medicine Service, KKH</i>
4.20 pm	<b>Updates in Management of Constipation in Children</b> <i>Dr Veena Logarajah, Consultant, Gastroenterology Service, KKH</i>
5.00 pm	End of forum

**Date**  
8 October 2016 (Saturday)

**Time**  
2.00 pm – 5.00 pm  
(Registration starts at 1.00 pm)

**Venue**  
KKH Auditorium (Training Centre),  
Level 1, Women's Tower  
100 Bukit Timah Road

**CME Points**  
2 points

**Fees**  
\$10 per pax  
(Lunch will be provided)

**Contact**  
Tel: 6394 8746

**Registrations by  
6 October 2016.**  
For more details, please call **6394 8746**  
(Monday to Friday, 8.30 am to 5.30 pm) or  
log on to [www.kkh.com.sg/events](http://www.kkh.com.sg/events). Seats  
are confirmed upon full payment on a first-  
come-first-served basis. Registration fee is  
non-refundable.






**SingHealth**  
[www.singhealth.com.sg](http://www.singhealth.com.sg)











### GP FAST TRACK APPOINTMENT HOTLINES

 Singapore General Hospital	<b>6321 4402</b>
 KK Women's and Children's Hospital	<b>6294 4050</b>
 Sengkang Health	<b>6472 2000</b>
 National Cancer Centre Singapore	<b>6436 8288</b>
 National Dental Centre Singapore	<b>6324 8798</b>
 National Heart Centre Singapore	<b>6704 2222</b>
 National Neuroscience Institute	<b>6321 4402/ 6357 7095</b>
 Singapore National Eye Centre	<b>6322 9399</b>

### DIRECT WARD REFERRAL CONTACT NUMBERS

 Singapore General Hospital	<b>6321 4822</b>
 KK Women's and Children's Hospital	<b>6394 1180</b>

### SINGHEALTH DUKE-NUS ACADEMIC MEDICAL CENTRE

 Singapore General Hospital	 KK Women's and Children's Hospital
 Sengkang Health	 National Cancer Centre Singapore
 National Dental Centre Singapore	 National Heart Centre Singapore
 National Neuroscience Institute	 Singapore National Eye Centre
 Polyclinics SingHealth	 Bright Vision Hospital