Medical Spotlight
Malignant Ovarian Germ Cell Tumour

Introduction
Germ cell tumours account for about 15-20% of all ovarian tumours. Of these, only 3% are malignant. This group of tumours is clinically important due to its occurrence in young women and treatment decisions that need to be taken that might affect future reproductive capabilities. These tumours bear certain common characteristic features: (i) all arise from the primitive germ cell of ovary (ii) they usually occur in younger patients (iii) although the most common site of germ cell tumours is the gonads, they can also occur at extragonadal sites along the route of migration of the germ cells from the yolksac to the genital ridge (iv) similar tumours are also found in males and (v) histologically different tumours can occur simultaneously within the same tumour quite commonly.

Among the ovarian germ cell tumours, mature cystic teratoma (dermoid) is the most commonly encountered. However, this is a benign tumour. Malignant germ cell tumours include dysgerminomas, immature teratoma, endodermal sinus tumours, embryonal cell carcinoma, polyembryoma, choriocarcinoma and mixed types. The WHO classification of ovarian germ cell tumours is given below.

Classification of Germ Cell Neoplasm of Ovary

Germ cell tumours
- Dysgerminoma
- Endodermal sinus tumour
- Embryonal carcinoma
- Polyembryoma
- Choriocarcinoma
- Teratoma
  - Immature (solid, cystic, or both)
  - Mature
    - Solid
    - Cystic
- Mature cystic teratoma (dermoid cyst)
- Mature cystic teratoma with malignant transformation
  - Monodermal or highly specialised
    - Struma Ovarii
    - Carcinoid
    - Struma ovarii and carcinoid
    - Others
- Mixed forms (above tumours in any possible combination)

Tumours composed of germ cells and sex cord stromal derivative
- Gonadoblastoma
- Mixed germ cell-sex cord stromal tumour

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Minimally Invasive Repair of Pectus Excavatum - The NUSS Procedure

A/Prof K Prabhakaran, Head & Senior Consultant, and Dr Vidyadhar Mali, Consultant, Paediatric Surgery, University Children’s Medical Institute (UCMI)

Pectus excavatum is a congenital depression of anterior chest wall due to abnormal concave or caved-in development of several ribs and sternum. The depth and degree of the depression determine the degree of cardiac and pulmonary compression. It is frequently noticed at birth and is progressive (slowly during early childhood and pronounced worsening during puberty). About one-third of such cases require surgical correction due to rapid progression of the deformity associated with deteriorating exercise tolerance and/or cardiac function.

Although the correction of this deformity previously required an extensive operation, it has now become possible to achieve satisfactory correction using a minimally invasive NUSS procedure whereby a convex metal bar is placed in the retrosternal space to elevate the concave depression. Thoracoscopic guidance ensures that the bar is placed accurately and safely in the retrosternal space without any injury to the heart or lungs.

The NUSS procedure has done away with cartilage incision, rib resection, sternal osteotomy and an open traumatic operation. Other advantages include minimal blood loss, short operating time and a comparatively rapid return to regular routine activity.

The procedure is also quite effective in correcting the cosmetic deformity as well as the physiologic impairment in exercise tolerance. Rather than just a cosmetic procedure, it is offered to patients with well-defined indications of effort intolerance. Further refinements in the bar metal, use of stabilisers and continued use of thoracoscopy add to the safety and efficacy of the procedure.

Surgical Treatment for Degenerative Scoliosis

A/Prof Hee Hwan Tak, Senior Consultant, Deputy Head, University Spine Centre, University Orthopaedics, Hand & Reconstructive Microsurgery Cluster (UOHC)

Degenerative scoliosis is defined as a condition in which the scoliotic angle caused by degenerative changes is greater than 10° using the Cobb’s method. This condition is usually located in the lumbar area and often accompanies loss of lumbar lordosis and lateral or ventral vertebral slippage at one or more levels. Degeneration of the facets and discs may lead to rotatory and translational listhesis which are the starting point that leads to scoliosis.

The most common indication for surgery in degenerative scoliosis is spinal stenosis not improving with conservative treatment e.g. medications, acupuncture, and physiotherapy. Back pain is a less common indication for surgical intervention. Decompression may result in excessive removal of facets, and thus the operation often includes fusion in situ or correction of the deformity plus fusion.

These patients are generally osteoporotic and securing a stable fixation with metal implants remains a challenge. Soft tissue contractures and the overall decrease in flexibility reduce the ability of achieving and maintaining correction. The elderly age of the patients adds to the additional surgical challenge and post-operative management. Medical co-morbidities may increase the complication rates in these patients.

The goals of surgical treatment are decompression of the neural elements and the achievement of a stable balanced spine. The severity and extent of the spinal stenosis and deformity will determine the extent of the surgical procedure needed.
Hoarseness is a common symptom seen in the practice of laryngology. Common diagnosis includes voice abuse, laryngitis, laryngopharyngeal reflux, vocal nodules, vocal cyst or polyp. However, it is important to rule out cancer of the larynx if the hoarseness remains persistent despite medical therapy.

Straboscopy is a technique which magnifies the image of the vocal cords in slow motion and therefore facilitates the clinician in diagnosing laryngeal pathology more confidently.

Managing patients with voice problems can be challenging as different patients have varying expectations on their voice outcome. Speech therapy is an important aspect in the management as it teaches patients on proper voice care and exercises, and helps to minimise recurrence of voice problems after treatment.

Surgery is the treatment of choice for several laryngeal pathologies, ranging from benign ones such as vocal polyp or nodules and even for early laryngeal cancer. Under magnification, the different layers of the vocal fold can be identified during excision of these lesions. Traditionally, excision of vocal cord lesions is performed with the use of cold instruments like microscissor and dissector.

However, many tertiary Otolaryngology centres have moved towards laser excision. Firstly, the use of CO2 laser allows precise excision of these lesions and hence, prevents unnecessary removal of the deeper layer of the vocal fold or vocal ligament. Secondly, CO2 laser does not penetrate deep into the vocal fold due to its wavelength properties and hence, minimise scarring post operatively.

Recently, CO2 laser excision has also been used to treat early laryngeal cancers with equivalent local control compared with radiation therapy. Patients are treated with a single modality in a day compared to a 4-6 weeks course of radiation therapy. Therefore, patients with early laryngeal cancer who are deemed suitable for laser excision are given this alternative in managing their disease.

Direct Access Endoscopy

Direct Access Endoscopy at the National University Hospital is a service available to the general practitioners who may wish to refer their patients for either gastroscopy or colonoscopy examination. The purpose of this service is to reduce the waiting time for an endoscopic examination. General practitioners can refer directly to the particular consultant or to obtain the earliest or the most convenient appointment for their patients.

Common indications for gastroscopy include epigastric pain, dyspepsia, and reflux. The most common indications for colonoscopy are PR bleeding, screening for colorectal cancer, positive faecal occult blood, chronic diarrhoea, and follow-up of colonic polyps.

The referring general practitioners will then subsequently receive a copy of the endoscopic report and recommendations for further management of their patients. This is to facilitate a continued care and follow-up for these patients by their general practitioners.
The spread of malignancy is mainly by the hematological and lymphatic channels and also by direct extension with seeding of abdominal cavity. Lung and liver metastasis are therefore more commonly associated with malignant ovarian germ cell tumours than with epithelial ovarian tumours.

Clinical characteristics

Germ cell malignancies are more common in Asians and Blacks (15% of all ovarian tumours) compared to the western population (5% of ovarian tumours), although the exact cause is not known. Ovarian germ cell tumours occur in females between the ages of 10-30 years.

In females younger than 20 years of age they represent two-thirds of all ovarian tumours of which one third are malignant. Clinically, these tumours are characterised by rapid growth. Symptoms and signs can occur from 1 day to 6 months with a median of 4 weeks. Patients usually present with abdominal pain and abdominal mass (85% of cases). This is probably why despite their rapid growth, they usually present in early stage disease. The pain can be attributed to rapid increase in size with capsular distension, haemorrhage and necrosis within the rapidly growing mass, rupture and torsion. Patients can also present with abdominal distension, fever and vaginal bleeding.

Germ cell tumours can rarely present with amenorrhoea and precocious puberty. This is more likely with tumours that express beta-HCG. Sometimes, raised beta-HCG may cause symptoms that mimic early pregnancy and cause delay in diagnosis. Germ cell tumours tend to be large with average size of about 15-16cm. They are rarely bilateral. Dysgerminomas can be bilateral in 12-19% of cases whereas endodermal sinus tumours are almost always unilateral. Ascites may be seen in advanced cases. Because it occurs in young women, it is one of the most common tumours occurring in pregnancy. Dermoid is the most common benign tumour occurring in pregnancy (40%) whereas dysgerminomas (20-30%) are the most common malignant tumours occurring in pregnancy.

Investigation

Germ cell tumours produce specific tumour markers which aid not only in diagnosis but also in evaluating response to treatment and recurrences. The table below shows the list of common tumour markers expressed by malignant ovarian germ cell tumours.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Common/specific tumour markers</th>
<th>Low level /less common markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>LDH, PLAP (placental alkaline phosphatase)</td>
<td>beta-HCG</td>
</tr>
<tr>
<td>Endodermal sinus tumour (Yolk Sac tumour)</td>
<td>AFP</td>
<td>LDH</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>-</td>
<td>AFP/LDH</td>
</tr>
<tr>
<td>Embryonal cell carcinoma</td>
<td>AFP/beta-HCG</td>
<td>-</td>
</tr>
<tr>
<td>Polycarcinoma</td>
<td>beta-HCG</td>
<td>AFP</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>beta-HCG</td>
<td>LOH</td>
</tr>
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</table>

CT scans can help in detecting lymph node involvement and intra abdominal spread, whereas chest x-rays can detect lung metastases. Karyotyping is needed in case of any ovarian mass > 2cm in premenarchal girls because of increased association with dysplastic gonads.

A 24-year-old presenting with pain and a 30cm pelvi-abdominal mass. Right salpingo oopherectomy done. Histopathology confirms a pure dysgerminoma of the right ovary.

Management

Staging of disease is the first step in the diagnosis and treatment of malignant germ cell tumours. Most malignant germ cell tumour present in early stage and this correlates with good prognosis. Commonly utilised staging system is the FIGO 1988 staging system. A unilateral salpingo oopherectomy with preservation of the contralateral ovary and the uterus is now considered the appropriate surgical management for patients with malignant ovarian germ cell tumour.

In patients with advanced disease, preservation of reproductive function is also possible, especially if the contralateral ovary is normal. Conservative unilateral salpingo oopherectomy has shown comparable disease survival when compared to bilateral salpingo oopherectomy with or without hysterectomy. Surgery alone is adequate for surgically staged and histopathologically confirmed stage IA pure dysgerminomas and low grade immature teratomas.

All other tumour types and stage will require adjuvant chemotherapy. Surgical staging includes assessment of peritoneal fluid cytology, biopsy of any suspicious areas on peritoneal surfaces, retroperitoneal lymph node sampling including pelvic and high paraaortic lymph nodes, and an infracolic omentectomy. The histopathological type and grade will need to be confirmed by frozen section during surgery. Biopsy of the contralateral, normal looking ovary is not indicated as it increases the risk of adhesions and can hamper fertility prospects. Also, these tumours are highly chemoinsensitive, so any occult disease can be managed with chemotherapy. In women who have completed their families, total abdominal hysterectomy with bilateral salpingo oopherectomy is advised. Optimum cytoreduction is associated with better adjuvant chemotherapy response as well as better progression free interval, especially so in nondysgerminomatous tumours.

Role of Chemotherapy

All other patients except those with stage IA pure dysgerminomas and low grade immature teratomas will need adjuvant...
chemotherapy. Most of the chemotherapy used in malignant germ cell tumours comes from the experience of managing testicular germ cell tumours. The VAC regime (vincristine, dacarbazine, cyclophosphamide) was the earliest regime to be used and its efficacy in incompletely resected advanced disease was poor11. Long term survival was 50% in nongerminomatous germ cell tumours of the ovary treated with VAC10. Following the success of cisplatin use in testicular germ cell tumours, regimes containing cisplatin came into use, like VBP (vinblastin, bleomycin, cisplatin) and BEP (bleomycin, etoposide and cisplatin)12, 13.

A GOG study in 1989 showed that VBP regime could achieve a successful salvage therapy of 70% overall 4-year survival 13. Because of the increased neurotoxicity of vinblastin, it was replaced with etoposide which was found to have less neurotoxicity with better efficacy, especially in bulky tumors 13. Five-year survival of ovarian dysgerminomas and 85% in nongerminomatous tumours can be achieved with the BEP regime, and it is now the most widely used regime12.

The National Comprehensive Cancer Network (NCCN) also recommends BEP regime for treatment of malignant ovarian germ cell tumours. Usually 3-4 cycles of BEP are given. According to a study by Gershenson on dysgerminomas as they have a propensity for late recurrences. For at least 5 years for nondysgerminomas, but at least 10 years for dysgerminomas treated with cisplatin or carboplatin based chemotherapy:A trial of malignant germ cell malignancies treated with cisplatin or carboplatin based chemotherapy:A Hellenic Cooperative Oncology Group Study.Gynecol Oncol 1996;62:70-4

Role of Radiotherapy

The role of radiotherapy in management of germ cell malignancy is limited. Of the germ cell malignancies, dysgerminoma is the most sensitive to radiotherapy. But due to the long term complication of radiation, damage to the preserved ovaries and availability of sensitive chemotherapy this modality is now almost never used.

Follow up

Most of the recurrences will occur within the first 2 years. There are no fixed follow-up regimes. In our centre, patients are followed up every 3 months in the first 2 years. Surveillance includes clinical history, examination, tumour markers and radiological examinations like chest X-rays and CT scan of abdomen only when necessary. Follow up provides not only an opportunity for early detection of recurrences but also to look out for late complications like gonadal failure, secondary malignancies like leukemia with etoposide use and pulmonary fibrosis with bleomycin use. Surveillance is advised for at least 5 years for nongerminomas, but at least 10 years for dysgerminomas as they have a propensity for late recurrences.

References

4. Schwartz PE, Chambers SK, Chamber JT, Kohorn E, McIntosh S. Ovarian germ cell malignancies: the Yale University experience. Gynecol Oncol 1992;45:26-31
Beta-adrenergic receptor blockers (beta-blockers) are commonly prescribed antihypertensive, anti-ischaemic and antiarrhythmic agents. In the past, they were contraindicated in patients with heart failure and impaired left ventricular systolic function because of their negatively inotropic effects that might precipitate or worsen heart failure. However, in the last 2 decades or so, several beta-blockers have been conclusively proven to improve symptoms, reduce re-hospitalisation and reduce mortality, especially sudden cardiac death, in patients with chronic systolic heart failure (CHF). Overall, these beta-blockers reduce all-cause mortality by up to 35%, sudden cardiac death by >40%, and reduce heart failure hospitalisations by >50%, as compared to standard therapy without beta-blockers. These agents are now Class I recommendations for treatment across a wide range of severity of heart failure. Yet, many studies have shown that these agents were under-prescribed in CHF populations, probably because of unfounded fears of adverse effects of beta-blockade. In this article, we continue with our FAQs on pharmacotherapy of CHF due to left ventricular systolic dysfunction, focusing on the use of beta-adrenergic receptor blockers based on our clinical experience and available data.

What is the rationale for the use of beta-blockers in the management of CHF?
Sympathetic nervous system (SNS) activation is one of the compensatory responses that occur in the syndrome of heart failure. These responses initially serve to increase cardiac output and maintain tissue perfusion. It has been shown that in heart failure, plasma and tissue concentrations of catecholamines such as noradrenaline are increased. Chronic activation of the SNS results in down regulation of beta-adrenergic receptors, desensitisation of the beta-adrenergic signal transduction system resulting in decreased myocardial contractile reserve, abnormalities of sarcoplasmic reticulum calcium cycling and many other biochemical and cellular abnormalities. These responses produce several deleterious effects on the cardiovascular system, including activation of the renin-angiotensin-aldosterone system (RAAS) and endothelin system, peripheral vasoconstriction and increase in ventricular afterload, increase myocardial oxygen demand and ischaemia, ventricular hypertrophy and dilatation, myocardial cell death and interstitial fibrosis, and increased arrhythmogenic potential with reduced threshold for ventricular tachyarrhythmias. Beta-1 receptor blockade has been shown to ameliorate these damaging effects of chronic SNS activation.

Many patients with heart failure also have tachyarrhythmias such as atrial fibrillation and ventricular tachycardia. Beta-blockers are crucial agents for controlling heart rates in CHF patients with atrial fibrillation, and to increase the threshold for ventricular tachyarrhythmias.

Do all beta-blockers produce the same benefits in chronic heart failure?
Unlike antagonists of RAAS (ACE inhibitors, angiotensin-II receptor blockers) whereby the benefits in CHF therapy with these agents appear to be a “class effect”, not all beta-blockers have been shown in randomised controlled trials to be beneficial in CHF. This probably stems from differences in the pharmacologic properties of the different beta-blockers in their beta-receptor selectivity, alpha-receptor blockade and other ancillary properties such as anti-oxidant and nitric oxide effects. Some beta-blockers have intrinsic sympathomimetic actions and these have not proven to be beneficial in CHF.

What are the beta-blockers that are recommended in chronic heart failure therapy?
Three beta-blockers, namely bisoprolol (Concor®), carvedilol (Dilatrend®) and extended release (ER) metoprolol succinate (Betaloc ZOK®), have been conclusively proven to produce benefits in CHF therapy and are approved for use for this indication. Bisoprolol and metoprolol are strongly beta-1 selective while carvedilol has both beta-1 and beta-2, as well as alpha-adrenergic receptor blocking properties. Nebivolol (Nebilet®) is a new non-selective beta-blocker that has recently been shown to produce a small reduction in outcomes compared to placebo in elderly patients with CHF, and is recommended in the European guidelines. Immediate release metoprolol tartrate (Betaloc®) was found in the Carvedilol Or Metoprolol European Trial (COMET) to be inferior to carvedilol in all-cause mortality risk reduction, although this result might be due to issues with trial design and inadequacy of beta-blockade in the metoprolol arm. However, because of the uncertain data associated with the use of metoprolol tartrate in CHF, we do not prescribe this in chronic systolic heart failure. Atenolol has not been studied in a randomised controlled trial to be beneficial in CHF.

What are the contraindications to beta-blocker therapy?
Beta-blockers should not be prescribed when the patient is acutely decompensated, in the presence of severe bronchospasm, hypotension and in patients with severe bradycardia or high grade atrioventricular block without a pacemaker.

How is beta-blocker therapy initiated?
In heart failure, beta-blocker therapy should be initiated only when the patient is stable, euvolemic and without evidence of hypoperfusion or hypotension. In the hospital, we usually initiate beta-blocker therapy when the patient’s acute decompensation has resolved and before discharge. This usually means that the patient would be on diuretics and an RAAS blocker. Instituting beta-blocker therapy prior to discharge may result in better adherence to therapy. The patient is monitored closely for any adverse effect, and dose adjustment made depending on tolerability. In the outpatient setting, most stable individuals in New York Heart Association (NYHA) functional class II-III can be safely initiated on beta-blocker therapy. The patient should be educated on potential adverse effects and encouraged to report any symptoms. Once therapy is initiated, we usually review the patient in 1 to 2 weeks’ time, depending on patient condition and potential risk of adverse effects.

Beta-blockers should be initiated at the lowest recommended dose: carvedilol at 3.125 mg once or twice daily, bisoprolol at 1.25 mg once daily, and ER metoprolol succinate at 25 mg daily. In our experience, the most common adverse reactions with initiation of beta-blockade in CHF are hypotension and worsening dyspnoea or effort intolerance. We accept blood pressures of 80/50 mmHg or more, provided the patient is symptom-free with no evidence of organ hypoperfusion. If the beta-blocker is well-tolerated, doses should be uptitrated slowly over several weeks and months, up to a maximum dose of 25 mg twice daily for carvedilol, 10 mg daily for bisoprolol and 200mg daily for ER metoprolol succinate.

How does one choose which beta-blocker to prescribe in heart failure?
The choice of beta-blocker depends on the severity of heart failure, left ventricular ejection fraction (LVEF), presence of other co-morbid medical conditions and the patient’s medication regimen. We usually
prescribe carvedilol in patients with compensated Class IIIb-IV heart failure, especially when the LVEF is <30%. In the COPERNICUS trial, carvedilol reduced the combined risk of death and hospitalisation by 24% compared with placebo in patients with severe heart failure and LVEF <25%. In the presence of well-controlled bronchospastic airway disease, we prefer to use the highly beta-1 selective bisoprolol. The patient’s medication regimen also influences the choice of agent. If the patient consumes medications only in the morning, once-daily bisoprolol may simplify the regimen. Patients accustomed to taking twice-daily medications may be prescribed carvedilol.

Which should be initiated first – a RAAS blocker or a beta-blocker in a patient with heart failure?

Historically, it was recommended that a RAAS blocker (ACE inhibitor or angiotensin receptor blocker) should be started first and beta-blocker should be instituted with background RAAS inhibition. In fact, provided it is safe to do so, both RAAS blocker and beta-blocker should commenced as early as possible. However, there are certain patients in whom we might defer RAAS blockade, chiefly those with renal impairment. Beta-blockers can be safely initiated first and when feasible, RAAS blocker prescribed at a later time. The CIBIS III study showed no significant difference in outcome whether bisoprolol was started first before enalapril, or enalapril commenced first before the addition of bisoprolol.

Can beta-blockers be prescribed in patients with asthma or chronic obstructive pulmonary disease?

Yes, highly beta-1 selective beta-blockers such as bisoprolol and metoprolol can be prescribed in patients with bronchospastic airway disease (BAD) provided the disease is well-controlled. Many patients with CHF are diagnosed with BAD based on a history of wheezing, cough and dyspnoea, but in actual fact these symptoms were manifestations of undiagnosed pulmonary congestion. Patients with concomitant CHF and COPD are at even greater risk of cardiovascular death, and beta-blockers are crucial to significantly reduce mortality in this group of patients. If the airway disease is well controlled with bronchodilators and the patient’s quality of life is not significantly impaired by respiratory symptoms, we would continue with the beta-blocker. Many patients with CHF and well-controlled BAD are able to tolerate maximal doses of bisoprolol and even carvedilol.

What if the patient experiences adverse effects while on beta-blocker treatment?

In the event of a life-threatening condition such as severe hypotension, bronchospasm and bradycardia, the beta-blocker must be discontinued and the patient treated accordingly. Once the patient has recovered and stabilised, we would usually attempt to reinitiate the beta-blocker at a lower dose. Patients with bronchospasm on carvedilol may be switched to bisoprolol or ER metoprolol. Permanent pacemaker implantation should be considered in those with severe bradycarhythmias so that the life-prolonging beta-blocker therapy can be continued. If a patient on beta-blocker experiences mild dec complication of heart failure, the beta-blocker dose should be halved while the patient is treated for the decompensation (usually with an increase in diuretic). It is important not to abruptly discontinue the beta-blocker unless absolutely necessary. Abrupt beta-blocker withdrawal leaves the upregulated beta-receptors exposed to endogeneous catecholamines and this may precipitate myocardial infarction, hypertensive crisis and tachyarrhythmias. Once the patient has stabilised, gradual dose uptritation may be instituted.

In stable outpatients who experience symptoms due to relative hypotension (usually dizziness after medications), we first evaluate the patient to exclude dehydration and other conditions that might cause hypotension. In the absence of these, we may reduce or discontinue other hypotensive agents such as calcium channel antagonists or nitrates. The beta-blocker dose may be halved and the patient observed for further symptoms. If the patient remains symptom-free, the dose may be uptitrated later. In patients who are on both RAAS blocker and beta-blocker and whose resting heart rates remain elevated (>80 beats a minute) with hypotensive symptoms, we usually reduce the dose of the RAAS blocker and persist with the beta-blocker dose. Elevated resting heart rate is an indication of persistent SNS activation. For other patients, we may spread out the medications over the day, for instance, prescribing the beta-blocker in the morning and the RAAS blocker in the evening to avoid hypotension.

Patient confidence in the medication may be affected once an adverse effect is experienced. It is important to educate the patient on the benefits of beta-blockers. Good rapport with the patient and/or care-giver, as well as a sympathetic and understanding physician goes a long way to re-establishing confidence.

Conclusions

Beta-adrenergic receptor blockers represent an important advancement in the treatment of chronic heart failure. With proper patient selection and vigilant patient monitoring, most patients with CHF can be prescribed and will tolerate these life-saving medications. We hope this article can help physicians to prescribe these medications and to maintain their CHF patients on long term beta-blocker therapy.
A Doctor's Heartbeat

Specialist in Focus

Professor Leong Peng Kheong Adrian
Deputy Director, National University Cancer Institute, Singapore (NCIS)

Dr. Adrian Leong is Professor of Surgery at the National University Health System (NUHS). He is currently Deputy Director and Head of the Division of Surgical Oncology at the National University Cancer Institute, Singapore (NCIS), as well as the Deputy Head of the University Surgical Cluster and Department of Surgery.

A Colorectal Surgeon by training, he maintains a special interest in the management of colorectal cancer and has spoken and published extensively on the subject. He was invited by the Ministry of Health to draw up the Clinical Practice Guidelines for the Management of Colorectal Cancer in Singapore. He also sits on the committee that is producing the current guidelines for Colorectal Cancer Screening. His other commitments in the field of cancer management in Singapore included sitting on the 3rd and 4th National Committees on Cancer Care. He currently sits on the Steering Committee of the National Colorectal Cancer Screening Programme.

At the National University Hospital, among his many portfolios, he was recently appointed Programme Director for the General Surgery Residency Programme. Nationally, in the field of postgraduate education, he has appointments to the Specialist Training Committee for General Surgery and the Joint Committee on Specialist Training.

Cancer has been widely recognised as a growing health problem, and the incidence of cancer is set to rise significantly as a result of lifestyle changes and an aging population in Singapore. In view of this, the Ministry of Health announced the setting up of the National University Cancer Institute, Singapore (NCIS) in 2007 as a national specialty centre to meet the rising demand for tertiary care in this field.

Professor Adrian Leong, Deputy Director, National University Cancer Institute, Singapore (NCIS), shares with us the Institute’s purpose and plans.

Tell us more about NCIS and its mission.

When we (the NCIS Executive Committee) first began to brainstorm about what NCIS could be and what it would do, we were impelled by the idea that we had a chance to build a world-class comprehensive cancer centre. By comprehensive I mean one that would focus on care of cancer patients as well as one that would engage in research and teaching. We saw that all three missions had to be viewed with equal importance. Like a three-legged stool, if one was shorter than the other two, the stool would be unsteady.

So our mission is firstly, to commit ourselves to outstanding patient care, secondly, to accelerate the process of translating medical discoveries into better ways of treating patients and thirdly, to make ourselves responsible for nurturing, training the next generation of cancer specialists and educating the public about cancer.

It's a tall order but I think one that is compelling enough to enthuse those of us who have chosen to dedicate ourselves to seeing NCIS’ mission come to fruition.

Could you share with us more about your work at NCIS?

Cancer services at the National University Hospital have a long history dating back twenty years or so. We have had excellent specialists in cancer surgery, haematology-oncology as well as therapeutic radiology. My contribution to this enterprise has been to see how all these specialists can come together in a way that makes access to the best care for patients as easy as possible. So my first task has been to take all the different elements that make up great cancer care and put them together so that our patients will benefit even more.

My second big task has been helping with the design of our new Cancer Centre in the forthcoming Academic Medicine Building. This will be built directly above the new Kent Ridge MRT station along the Circle Line. NCIS is going to be an anchor tenant. I have been excited by the process of planning and the prospect of seeing that big hole in the ground next to the National University Hospital’s Kent Ridge Wing become a 20-storey building with a state-of-the-art Cancer Centre nestled right in the heart of it. Work on this has been demanding but I am really grateful for the help from the wonderful team at NCIS. The level of detail that we have gone into, in order to provide both patients and staff with a great facility, is amazing.
What are the more common conditions that NCIS specialists see?

That’s a hard one to answer because no patient with cancer is turned away at NCIS, so the spectrum of cancer cases that are seen at NCIS is vast.

Our focus has been on nine tumour types. These can roughly be broken down into three categories. The first group consists of cancers with a high frequency in Singapore, such as cancers of the breast, lung, colorectum, stomach and prostate.

The second group are cancers with an ‘Asian phenotype’, that is cancers that may behave somewhat differently here as compared to the west or have a higher frequency than in other parts of the world. These include cancers of the liver and nasopharynx.

In the last group are cancers that we have a particular expertise in, namely haematological and gyaecological malignancies.

In recent years, there has been a shift in the focus from cancer treatment to preventive measures such as public education and health screenings. More funds have also been channelled towards research on the reasons why certain cancers develop.

What are your views on this shift?

I have been a big proponent of prevention in the field of cancer for more than a decade. My belief, and this is supported by some evidence, is that the biggest improvement in our attempts to reduce death from cancer in Singapore will come from detecting cancer at a pre-malignant or at an early stage. Statistics show stage for stage, our cancer survival is comparable to that of any developed country. However, when the population is taken as a whole, survival is worse. This means that although our treatment for cancer is good, our patients are presenting at a later stage of their cancer compared to those in other developed countries. In my specialty, colorectal surgery, there is clear evidence that screening will reduce your chance of dying from colorectal cancer.

The big challenge is getting these preventive programmes going and getting people to participate. That is why NCIS has made public education a special area of focus. We are starting in a small way by adopting a specific community in Taman Jurong to see how some of these barriers to screening and access to medical care can be overcome.

What are the significant developments in your field that have resulted in better treatment for patients?

When I first returned from my HMDP fellowship in 1992, I brought back a technique known as Total Mesorectal Excision for rectal cancer. This technique results in the lowest recurrence rate following rectal cancer surgery. Although it was practiced in some form prior to that time, I like to believe that I contributed by clarifying and popularising the technique, which has become standard of care. For many years, this was done by traditional open surgery involving a long midline incision into the abdomen. Now we can do this via laparoscopic as well as robotic surgery. The improved visualisation, surgical access and precision of dissection using these technologies are dramatic. The reduced length of surgical wound and increased speed of recovery are also benefits for the patient. So in the field of surgery, technology has been a big driver of significant developments.

How do you see cancer treatment developing in Singapore?

One thing that I have come to understand is that trends in medical care have been driven by what everyone wants. To name a few – drugs without side-effects, surgery without pain, treatment with no interference with the rest of our lives. So increasingly, that is what we will see – more targeted treatments, less invasive surgery and hospital and clinic systems that do not require you to spend the whole day or days in a medical facility.

Of course, we’re not there yet. But you see it happening. Recall what things were like one to two decades. I think you’ll see what I mean.

Finally, what are some plans that NCIS has mapped out for the next 10 years?

We will be expanding our space and facilities in the Kent Ridge Wing of the National University Hospital (NUH). There will be more consultation rooms and chemotherapy treatment chairs. This will help manage the increase in patient numbers that we are seeing. This new space will also give us the opportunity to run multi-disciplinary tumour clinics.

In 2013, the new Academic Medicine Building with NCIS occupying three levels should be up and running. We will have all our ambulatory cancer services located in one place. Other than areas for consultation and chemotherapy infusion, the cancer centre will also house our latest linear accelerators to provide radiation therapy. We have designed it so that everything to do with cancer care will be ‘under one roof’. There will be an operating theatre complex located just one floor above us. This will permit us to do day procedures for our patients.

We ran a survey of our cancer patients to ask them what they would like to see in a cancer centre. One of the top requests was for a place to learn more about their cancer. We have listened. There will be a Health Resource Centre that will not only house a library with cancer-specific educational materials but will also be a venue for cancer-related talks. We have set aside space for a meditation room, an exercise area as well as for a space for counselling patients on dealing with their disease. We are taking this idea of holistic care seriously.
Liver Cancer - Its Early Detection and Treatment

A/Prof Krishnakumar Madhavan, Senior Consultant and Head of Liver Tumour Group, National University Cancer Institute, Singapore (NCIS)

Introduction

There are two types of liver cancer — primary and secondary. While it was thought that secondary cancers of the liver far outnumber the primary ones, this may not be true in Southeast Asia where the incidence of primary liver cell cancers (Hepatocellular carcinoma) is extremely high. It is now well known that the cirrhosis of the liver is a predisposing factor for the onset of cancer in the liver. It is also true that those with hepatitis B and C infections are even more prone to developing cancer of the liver.

Liver cancer is one of the most common cancers in Singapore. The incidence is much more in men but increasingly occurs also in women. Without early diagnosis and appropriate treatment, the disease is invariably fatal. Without treatment, few patients are able to survive five years after diagnosis.

Unfortunately, unlike other cancers, there may be no symptoms in the early stages. Diagnosis is often made very late when no chances exist for effective treatment.

If diagnosed in the early stages, many patients can still be cured through close follow-up. Regular tests and scans will be required for many years, often on a lifelong basis. The high incidence of liver cancer in Singapore is mostly attributed to the prevalence of viral hepatitis in the population. Subsequently, following the successful vaccination campaign by the Government, there was a drop in the number of cases of viral hepatitis.

A high level of public awareness about the disease of viral hepatitis and the importance of regular follow-up, blood tests and scans is essential to diagnose the condition early and thereby maximise the benefit for the patient. Similarly, it is imperative that all newly diagnosed patients are discussed in a multidisciplinary setting so that the most appropriate treatment for each patient is charted and recommended. General Practitioners and Polyclinic doctors should also be aware of the importance of regular follow-up and protocol to investigate patients who are hepatitis carriers in their practice.

Surveillance and early diagnosis

There should be close follow-up for all patients with known viral hepatitis (B or C) or HBV and HCV infections. This should include a physical examination and blood test for the tumour marker Alfa Feto protein (AFP). In addition, an ultrasound examination of the liver should be done every three to six months. With this regular regime of follow-up, most cancers can be diagnosed early.

The liver is a site for many abnormal shadows, most of which may be benign and harmless. If the ultrasound examination reveals any abnormality in the liver, the patient should either be sent for a more objective scan (CT scan or MRI scan) or sent to a hospital for consultation with a hepatologist or a hepatobiliary surgeon. The CT scan or MRI scan will throw more light on the liver lesion and allow appropriate action to be initiated.

Along with the scans, blood tests are conducted for the amount of viral load in the patient so that a decision can be made for the need for any antiviral treatment.

Unlike many other cancers, a biopsy of the suspected liver cancer is not often undertaken. The diagnosis can often be made without a biopsy by the tumour marker AFP and also the characteristics of the lesion on the CT scan. Rarely is a biopsy required to confirm the diagnosis. Moreover, the biopsy has a risk of spreading the tumour, which may jeopardise subsequent treatment. Whenever a curative treatment is not possible due to any reason, and especially when the patient is considered for various clinical trials involving non-surgical treatments, a biopsy proof of diagnosis may be mandated.

Treatments for Hepatocellular carcinoma

Surgical treatments (liver resection and liver transplantation)

For many years the only “curative” treatment available for liver cancers was surgical resection. This often required major surgery but more recently, laparoscopic or minimally invasive methods have been developed. The age, other illnesses or indeed the poor functional reserve of the liver from underlying cirrhosis often precluded surgery in these patients. On average, only 10 – 30 % of all patients referred for possible surgery were eligible for the same. The initial surgical results were poor with many post-operative complications and mortality following surgery up to 10 – 15%. Through good patient selection as well as surgical and anaesthetic advances, this has been reduced to acceptable levels of around 5%.

Clearly, many factors play a role in the success or otherwise of surgical treatment including the patient condition, tumour factors and the extent of surgery. Surgical resection was clearly not indicated in those patients with very poor liver function (Child’s C cirrhosis). In these patients, only a liver transplantation would suffice. Liver transplantation initially had very poor results as only the unresectable patients were transplanted. Currently liver transplantation is restricted to those with small tumours as well as those with fewer tumours. In Singapore, the criteria used to allow transplantation is known as the UCSF criteria. Unfortunately in most countries, waiting for cadaveric liver donor means a long waiting time on the waiting list.

During this time, the tumour can grow and depending on the duration of the wait, a small number of such patients can drop out of the waiting list. In most centres, liver transplant is seldom offered as the first line of treatment except for those patients with extremely poor liver function. Instead, it is usually offered when following an initial resectional surgery, tumour recurs in the remaining liver. This...
The recipient’s liver does not work, it may be morally very difficult.

There is rigorous debate over whether centres should accept such
the recipient has cancer outside the criterion of acceptability.

There is an ethical dilemma when a living donation is offered and
under restrictive criteria, recurrence of tumours is minimal.

resection makes subsequent transplantation more difficult and
technically challenging, and this may result in a higher incidence
of complications and mortality. When transplantation is performed
under restrictive criteria, recurrence of tumours is minimal.

Finally, the latest breakthrough in the treatment of liver cancer has
come through what is popularly called “Targeted therapy”. This is
treatment using drugs that are antibodies and small molecules that
disrupt with the normal mechanisms of cancer growth. The most
popular drug in this category is Sorafenib. It has already shown
significant effects and survival advantage in advanced hepatocellular
carcinoma and, clinical trials are under way to test its effectiveness
in curing or prolonging cure in early cases. Although these drugs
are available in the market at expensive rates, they should be used
only under clinical trials till the benefit is unequivocally established.

Strategy for the Future

The results of resection and liver transplantation for liver cancer
are unlikely to improve much more than at present. Similarly, the
proportions of patients who will benefit from the surgical modalities
with a cure are also likely to remain small. The near future will focus
on research on early diagnosis (better biomarkers, biomarkers that
prognosticate future tumour behavior and drug responsiveness) and
in maximising the results of non-surgical treatments. While more
and newer drugs will be developed, it will take time and trials to
establish the role of each in its rightful place in treating liver cancer.
In the meantime, we owe it to our patients to maximise their benefit
from existing treatment modalities. To this end, the treatment for
each patient should be discussed in a multi-disciplinary setting and
the most appropriate modality chosen for each.

Non-surgical treatments

Given an equal choice between surgical and non-surgical
treatments, most people would choose non-surgical treatment. Till
recently, although many modalities of non-surgical treatment exist,
they were all considered inferior to surgical treatment and in effect,
only palliative. More recently however, some randomised controlled
studies have been undertaken and some ablative techniques have
been found to give results similar to surgery.

Moreover, they have the benefit of reduced morbidity and mortality,
and the ease of the procedure, most of which can be undertaken
as out-patients. Over the years, local ablative techniques that were
tried include cryosurgery, thermal ablation, microwave ablation
and injection of ethanol into the tumour. Currently, however, the most
popular among these is radio frequency ablation (RFA). Although
initially confined to treating small tumours, innovations in delivery
and needle design have now enabled treatment of multiple and larger
lesions with excellent results. If the tumour is not fully ablated in one
session, or recurs in the ablated area, repeat procedures can be
undertaken effectively. The radiofrequency energy can be delivered
either radiologically in the X-ray department or laparoscopically or,
directly at open surgery.

The other modality of non-surgical treatment that has gained
popularity is trans-arterial chemo embolisation (TACE). This has
traditionally been used as a palliative modality as cure is seldom
achieved. However examples of “stable” cancer for long periods
of time are well documented. In addition to chemotherapy, beads
of active cancer drugs and radioactivity have also been delivered
using angiographic approach. Combinations of different modalities
or using one on the failure of another will form the strategy for the
treatment of many of these patients.

A/Prof Krishnakumar Madhavan
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National University Cancer Institute,
Singapore. He is also Head and Senior
Consultant of Division of Hepatobiliary
and Pancreatic Surgery at the National
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In addition to all aspects of liver transplantation, A/Prof Madhavan
has extensive experience in kidney and pancreatic transplantation
and also the whole spectrum of benign and malignant hepatobiliary
and pancreatic surgery.

His current research interests include the role of chemoembolisation
in the management of hepatocellular carcinoma, management of
cholangiocarcinoma, role of portocaval shunting in Piggy-back liver
transplants, various aspects of live donor liver transplantation and
saphenous venous peritoneal shunting in intractable ascites due to
cirrhosis of liver. He is a co-author of many papers pertaining to his
field of interest.

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For any advice or service relating to patients with hepatocellular carcinoma / liver cancer, you may contact our HCC coordinator from the
National University Cancer Institute, Singapore (NCIS).

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Upcoming Events

NUH GP CME Programme - in 2010
For enquiries & registration, please contact GP Liaison Centre (GPLC) at 6772 2535, or, email to gp@nuhs.edu.sg

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<td>Surgery Management of Incidental Liver Lesions</td>
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<td>23 Jan</td>
<td>Ophthalmology Dry and Wet Eyes in Children and Adults - Evaluation and Management of Cornea / Oculoplastics</td>
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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 prerogative to make appropriate changes should the need arises. Please refer to our events calendar at www.nuh.com.sg/gplc.html for more updates and information.

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