ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

DIAMOND JUBILEE CELEBRATION 1957-2017 60 years

VOLUME 46 | NUMBER 1 | FREE PAPERS | JANUARY 2017

MCI(P) 022/11/2016

"One does not meet oneself until one catches the reflection from an eye other than human."

Loren Eiseley (1907 – 1977)
American scientist

Reproduced with permission from:
A/Prof Chen Fun Gee

Please see inside Contents for the full list of articles.

Editorial

Overcoming Ethical Challenges of Bedside Medical Education

Duu Wen Sewa, [1]*MRCP (UK)*, Devanand Anantham, [1,2] *FCCP*

Introduction

Bedside teaching has long been a time-honoured component of medical education, and this was emphasised by Sir William Osler, father of modern medicine who once said, "To study the phenomena of disease without books is to sail an uncharted sea, while to study without patients is not to go to sea at all." While utilitarian arguments have been used to justify such training, deontological ethics mandate that we do not arbitrarily use teaching subjects as means to an end.[1] Patients are under no obligation to participate in medical education and their involvement remains an act of altruism. The moral burden of practising on patients lies with our profession and the challenge is to educate without compromising either the rights or safety of patients.

The Seven Ethical Requirements

It is necessary to consider an ethical framework to justify bedside medical education in terms that can be directly addressed to the subjects themselves, i.e. patients.[2] We propose such a framework, adopted from Emmanuel et al[3] on ethical requirements in research, which shares an analogous moral dilemma: balancing individual risk for third part benefit.[3] The 7 ethical requirements that were identified are: 1) social value, 2) validity, 3) fair subject selection, 4) favourable risk-benefit ratio, 5) independent review, 6) informed consent and, 7) respect for subjects.[3]

Value

Social and clinical value is an ethical requirement because finite resources need to be managed responsibly and to avoid exploitation.[3] Bedside medical education must not expose teaching subjects to potential harm without some possible social or clinical benefit. The value of bedside teaching has been well extolled in the literature, including learning in context, increasing learners' motivation and nurturing of clinical reasoning. In addition, it provides opportunity for role modelling, professional thinking, observation of communication skills and teamwork and the integration of these various skills in the process of patient care.[4]

Validity

Clinical education needs to be based on sound pedagogical principles to be ethical. Poorly planned teaching will lead to limited benefits to learners even if the skills being taught are important. The justification for validity is the same as value, i.e. avoidance of exploitation and management of finite resources.[3] Strategies to improve the effectiveness of bedside teaching can be briefly categorised into stages that can be carried out sequentially before rounds, during rounds and after rounds (Table 1).

Table 1. Strategies Involved in Bedside Teaching That Will Increase Validity

Stages	Key Strategies	Details of Strategies
Pre-rounds	Preparation	Familiarise with clinical curriculum[5]
		Understand learner's knowledge, clinical skill level and needs
		Set learning objectives for the session
	Planning	Decide on teaching methods[6]
		Select appropriate patients
		Set aside protected teaching time
	Orientation	Set learner expectations and roles during the patient encounter
Rounds	Introduction	Introduce team to patient, emphasising nature of the encounter
	Interaction	Role model a physician-patient interaction[7]
	Observation	Keen observation of learner interaction with patient
	Instruction	Teach in a non-humiliating, non-judgemental way
Post-rounds	Summarisation	Tell the learner what has been taught
	Debriefing	Discuss the bedside encounter
	Feedback	Review with learner what went right or badly
	Reflection	Gain insights from the encounter to help prepare for the next teaching session[6]

[1]Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore
[2]Duke-NUS Graduate Medical School, Singapore
Address for Correspondence: Dr Sewa Duu Wen, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Outram Road, Singapore 169608.
Email: sewa.duu.wen@sgh.com.sg

Fair Selection of Subjects

Patients who are included or excluded from teaching and the strategies used for selecting them are addressed by this requirement. Fair selection requires that teaching aims (and not vulnerability or privilege) to be the basis for choosing teaching subjects. Convenience is not a justifiable reason for choosing who will be practised upon because efficiency cannot override fairness.[4] If a group of patients is unlikely to gain from teaching, then this group should be excluded as teaching subjects. The poor, socially vulnerable, poorly educated and those lacking decision-making capacity cannot bear a disproportionate burden for the wealthy, educated and privileged to enjoy the benefits.

Favourable Risk-Benefit

The potential for risk to a patient who is taught upon must be minimised and any possible benefits maximised. Use of simulators, peer physical examination and non-patient volunteers can prepare learners to gain competency before their first real patient encounter.

Risks of procedures performed by trainees can be minimised by attentive supervision especially in the early stages of training.[8] This is supported by data that such supervised procedures can have equivalent outcomes to those performed by qualified staff.[9]

Enhancement of benefits to teaching subjects should be linked to their health and not financial inducements or additional unrelated medical benefits. There is qualitative data suggesting patients value the companionship and the relief from loneliness due to longer contact time.[10] Talking about their illness may help patients gain insight into their condition and about the training of doctors.[11] There is also the satisfaction of altruism and of having contributed to something of genuine value in service to the community.[12]

Independent Review

Curriculum and pedagogy review by experts and stake holders is not yet routine. This procedural requirement ensures that medical schools are following ethical requirements and helps openly manage conflicts of interests. All these safeguards must be preserved without compromising the equally important public interest that doctors should attain competence before they qualify. To achieve these aims, the members of the review board should understand medical science, pedagogy, ethics, and law, as well as represent the values, concerns, and priorities of the population from whom the teaching subjects will be chosen.

Informed Consent

Informed consent champions the autonomy of patients to ensure that their decisions are consistent with personal values, interests, and preferences. It requires patients to be provided with information in the context of their medical condition to enable them to make voluntary decisions about involvement in teaching without manipulation or coercion. Patients should be informed in advanced about teaching sessions and not feel pressured to decide at short notice.[13] Studies have shown that patients even want to be explicitly asked before students were allowed into surgical theatres as observers and before students have any access to medical records.[14] Patients need to be counselled of their right to refuse to see students without fear of abandonment by their physicians. However, evidence suggests that most patients will allow medical students to perform clinical evaluations and minor procedures even when informed of the student's inexperience.[15] While patients have expressed their desire to be explicitly informed if it is the first time that the student is performing the procedure,[16] they are more likely to consent if there is already established rapport.[17]

Special challenges exist for patients with persistent mental incapacity. Substituted judgement standard can be used in previously-competent adults (e.g. geriatric populations) and best interest standard can be used in never-competent individuals (e.g. paediatric patients) by the relevant healthcare decision-making proxies. Strict guidelines should also be in place and compliance checked when circumstances such as medical emergencies make it impossible to obtain consent.

Respect for Patients

Respect for patients goes beyond obtaining informed consent and is the affirmation of individual dignity. It requires sensitivity to preferences and values without prejudice.[18] This is achieved by ensuring privacy, allowing them to change their minds with regard to participation at any time without fear of repercussion and monitoring their welfare throughout the session. A patient-centred approach changes the role of the patient from a passive "interesting case" to one where they serve as a teacher. They can be trained as facilitators in the development of clinical skills and attitudes.[10] Treating patients as teachers recognises the value of their contributions and will increase the respect accorded by both clinicians and students.

Conclusion

The therapeutic needs of patients and the learning needs of students do not necessarily have to be in conflict. Instead, a compromise must be sought where both can be safely and justifiably met. Most patients have found their experience

with medical education a positive one and most felt that trainees did not undermine the standard of clinical care. Understanding the ethical requirements of bedside medical education as outlined in this editorial will help us to find ways to overcome the various ethical challenges in this area.

REFERENCES

1. Hamilton P. Ethical dilemmas in training tomorrow's doctors. Paediatr Respir Rev 2006;7:129-34.
2. Chiong W. Justifying patient risks associated with medical education. JAMA 2007;298:1046-8.
3. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000;283:2701-11.
4. Cox K. Planning bedside teaching–1. Overview. Med J Aust 1993;158:280-2.
5. Ende J. What if Osler were one of us? Inpatient teaching today. J Gen Intern Med 1997:12:S41-8.
6. Nair BR, Coughlan JL, Hensley MJ. Student and patient perspectives on bedside teaching. Med Educ 1997;31:341-6.
7. Jagsi R, Lehmann LS. The ethics of medical education. BMJ 2004;329:332-4.
8. Bernstein M, Knifed E. Ethical challenges of in-the-field training: a surgical perspective. Learn Inq 2007;1:169-74.
9. Pace DE, Chiasson PM, Schlacta CM, Mamazza J, Poulin EC. Laparoscopic splenectomy: Does the training of minimally invasive surgical fellows affect outcomes? Surg Endosc 2002;16:954-6.
10. Stacy R, Spencer J. Patients as teachers: a qualitative study of patients' views on their role in a community-based undergraduate project. Med Educ 1999;33:688-94.
11. Benson J, Quince T, Hibble A, Fanshawe T, Emery J. Impact on patients of expanded, general practice based, student teaching: observational and qualitative study. BMJ 2005;331:89.
12. Coleman K, Murray E. Patients' views and feelings on the community-based teaching of undergraduate medical students: a qualitative study. Fam Pract 2002;19:183-8.
13. Benson J, Quince T, Hibble A, Fanshawe T, Emery J. Impact on patients of expanded, general practice based, student teaching: observational and qualitative study. BMJ 2005;331:89.
14. Leung GK, Patil NG. Medical students as observers in theatre: is an explicit consent necessary? Clin Teach 2011;8:122-5.
15. Olson LG, Hill SR, Newby DA. Barriers to student access to patients in a group of teaching hospitals. Med J Aust 2005;183:461-3.
16. Santen SA, Hemphill RR, McDonald MF, Jo CO. Patients' willingness to allow residents to learn to practice medical procedures. Acad Med 2004;79:144-7.
17. Santen SA, Hemphill RR, Spanier CM, Fletcher ND. 'Sorry, it's my first time!' Will patients consent to medical students learning procedures? Med Educ 2005;39:365-9.
18. Entwistle VA, Carter SM, Cribb A, McCaffery K. Supporting patient autonomy: the importance of clinician-patient relationships. J Gen Intern Med 2010;25:741-5.

Original Article

Management and Outcomes of Fetal Hydrops in a Tertiary Care Centre in Singapore

Xin Yi Thong, [1,2]*MBBS (S'pore)*, Le Ye Lee, [1,3]*MMed (Paeds), MRCPCH (UK)*, Dawn AK Chia, [4]*DCR(UK), DMU(UK)*, Yee Chee Wong,[4]*MBBS (S'pore), MMED (O&G, S'pore), FRCOG (UK)*, Arijit Biswas, [4]*MD, FRCOG, FAMS*

Abstract

Introduction: Fetal hydrops is a serious condition which can be caused by immune and non-immune aetiologies. We aimed to review the management of fetal hydrops at our hospital. Materials and Methods: A retrospective review of all cases of fetal hydrops diagnosed in our institution from 2006 to 2013 was carried out. Results: Out of the 30 cases of fetal hydrops diagnosed antenatally, 17 were cases of Bart's hydrops which were all terminated in-utero. Of the remaining 13 cases, 11 cases consisted of non-immune causes of hydrops. Planned antenatal interventions including in-utero blood transfusions (n = 4) and thoracentesis (n = 5) as well as planned caesarean deliveries (n = 11) were performed in the majority of cases. Postnatal neonatal intensive care with interventions including chest drainage and transfusions were also performed. A majority, 92%, of the cases survived the perinatal period following a variable length of hospital stay ranging from a week to 3 months. Conclusion: Management of fetal hydrops is complex. Close coordination between the obstetric and neonatal teams was the key to good short-term survival of neonates with antenatally diagnosed hydrops, as it allows timely antenatal intervention and anticipation of potential perinatal complications.

Ann Acad Med Singapore 2017;46:4-10

Key words: Antenatal, Complications, Interventions, Non-immune, Survival

Introduction

Fetal hydrops, or hydrops fetalis, is a serious antenatal finding, with several studies around the world quoting similar perinatal survival rates of only 40% to 50%.[1-5] It indicates the presence of excessive fluid in 2 or more fetal compartments, which can include the abdominal cavity, pleural space, pericardial space, and subcutaneous tissue. The aetiology can be divided into immune and non-immune causes. Immune-mediated hydrops fetalis is typically due to fetal anaemia resulting from red blood cell alloimmunisation between mother and fetus.[3] Non-immune hydrops, on the other hand, is defined as the presence of fetal subcutaneous tissue oedema associated with a significant effusion in one or more cavities in the absence of atypical red cell antibodies[2] and has been the main cause for fetal hydrops for more than a decade.[1,3,6] Common causes include fetal cardiac arrhythmias, vascular and lymphatic malformations causing circulation obstruction, chromosomal abnormalities and metabolic conditions such as lysosomal storage diseases.[7,8]

Despite the ability to identify this condition early from the antenatal period, the morbidity and mortality rates from hydrops fetalis reported in current literature are often significant. However, with the advent of in-utero fetal therapy, the experience in our centre has been different, with positive outcomes in most of our cases of non-immune hydrops, apart from those with Bart's hydrops. This prompted us to do a detailed retrospective case series study, in an attempt to review the outcomes of in-utero treatment of fetal hydrops from our hospital. We hoped to understand the strength in our areas of management of hydrops fetalis

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University Singapore, Singapore
[2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore
[3]Department of Neonatology, National University Hospital, Singapore
[4]Department of Obstetrics and Gynaecology, National University Hospital, Singapore
Address for Correspondence: Dr Thong Xin Yi, Department of Paediatrics, 5 Lower Kent Ridge Road, National University Hospital, Singapore 119074.
Email: xin_yi_thong@nuhs.edu.sg

that could be pivotal in positively influencing survival outcomes for these children.

Materials and Methods

We conducted a retrospective review of all the cases of fetal hydrops diagnosed via antenatal ultrasound at the Fetal Care Centre in National University Hospital (NUH) from 2006 to 2013. Cases were obtained from the database of records from the Obstetrics and Gynaecology Department, NUH, which is a tertiary referral centre. The approval from the Domain Specific Review Board (DSRB) was obtained for the study.

Of the total of 30 cases of hydrops diagnosed, 17 pregnancies were cases of Bart's hydrops, due to alpha thalassaemia major. These 17 cases were terminated in-utero after confirmation of the Bart's hydrops with genotyping performed prior to the development of hydrops. The case records of the remaining 13 cases were then studied in detail from diagnosis to the perinatal period until discharge or death of the infant. None of these 13 cases defaulted or were delivered in another healthcare institution, hence there were no dropouts.

Identification of Hydrops

Antenatal scans were performed by trained ultrasonographers who are either certified by the American Registry for Diagnostic Medical Sonography (ARDMS) or who hold a diploma in Diagnostic Medical Ultrasound (DMU). The scans were performed using either General Electrics (GE) Voluson 730 Expert or GE Voluson E8 machines, both of which are manufactured in California, United States of America. Scans performed were then verified by the consultant obstetricians (Wong YC or Biswas A). Inclusion criteria for the 13 cases were ultrasound findings of excessive fluid in at least 2 preformed spaces of the fetus (ascites, pleural effusion or pericardial effusion), or fluid in 1 preformed space associated with skin oedema.

Antenatal Investigations to Identify Aetiology

Maternal medical and past obstetrical histories were reviewed for possible aetiologies for hydrops. Maternal antenatal testing results were reviewed and these included tests for in-utero infections such as tests for hepatitis B (HBsAg, HBeAg), human immunodeficiency virus (HIV) via antigen-antibody screen, syphilis (VRDL and TPR) and TORCH screen (comprising serology for antibodies against toxoplasmosis and rubella, PCR for cytomegalovirus and for herpes simplex). Other maternal results reviewed included maternal tests for anaemia, thalassaemia, blood group, rhesus typing and also antibody titres that were performed routinely.

Fetal antenatal investigations reviewed included chromosomal karyotype in the survivors and thalassaemia genotyping obtained via chorionic villus blood sampling for those with Bart's hydrops. Antenatal ultrasound assessments were reviewed for any possible structural abnormalities, in particular major cardiac malformation and cardiac rhythm abnormalities and other structural malformation in the thoracic and also renal malformations were performed for all cases. In cases with anaemia, fetal doppler assessment of blood velocity in the fetal middle cerebral arteries (MCA) was used for assessment. Cordocentesis was performed in all those cases with fetal anaemia when the peak systolic velocity of the MCA exceeds more than 1.5 MoM (multiple of median). Confirmation of fetal anaemia and investigations to determine the aetiology of the anaemia were performed prior to blood transfusions. Placental abnormalities were also examined to determine potential causes of hydrops. Follow-up ultrasounds were performed 2 to 4 weekly to monitor the fetal condition in-utero and the progression of the hydrops, depending on the in-utero treatment required. In addition, the various in-utero treatments undertaken were also reviewed.

Neonatal Investigations and Data Collection

The neonatal medical records were reviewed to identify the possible aetiology of hydrops, the perinatal resuscitation required and outcomes such as Apgar scores and level of metabolic acidaemia on blood gas, neonatal course and ventilation mode required, postnatal evaluation and investigations, the treatment required including blood transfusion, thoracocentesis and surgical treatment if needed, the length of stay and eventual survival outcome. None were first diagnosed postnatally as neonatal intensive care admission records for the last 7 years were also counter-checked to identify any undiagnosed cases. Laboratory investigations performed in the neonate to determine the aetiologies of hydrops were also reviewed and these included full blood count, rhesus and blood type, liver function tests, urea, creatinine and also assessment for TORCH and parvovirus infections. Neonatal procedures reviewed included cardiac assessment including echocardiography and cardiac rhythm monitoring. Chest x-rays and pleural fluid, if present, were sent to determine for triglycerides, protein analysis and microbiology. Abdominal x-rays and contrast studies were performed for those with suspected gut atresia prior to surgical explorations.

Statistical Analysis

Statistical analysis was performed using SPSS version 20 from IBM. Continuous data were described as mean

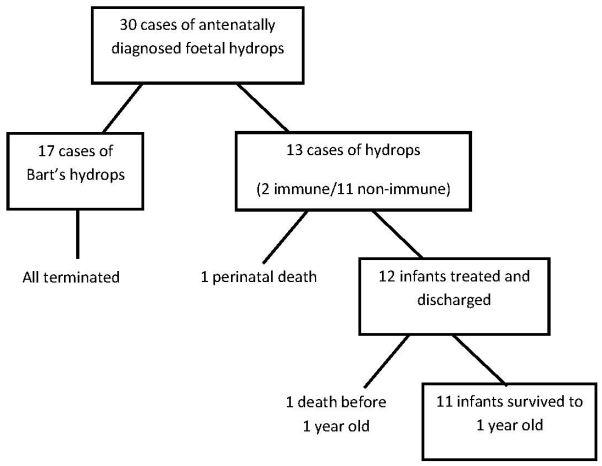

Fig. 1. Chart showing the study subjects.

with its standard deviation or median with appropriate range, while absolute and relative frequencies were used for categorical values. Chi square tests were performed to compare the dichotomous data between the fetus received in-utero therapy and those that did not. Descriptive data was presented for the comparison with the other 2 published studies. A *P* value of less than 0.05 was considered to be statistically different.

Results

Antenatal Diagnoses and Management

Of the 30 cases of hydrops, the most common aetiology was found to be due to Bart's hydrops, as confirmed on chorionic villus sampling and genetic sequencing for alpha thalassaemia in 17 cases (56.7%) (Fig. 1). These 17 cases were terminated in-utero.

All of the remaining 13 cases of fetal hydrops were delivered at late preterm period. Demographics of the neonates at birth are shown in Table 1. Diagnosis was made via ultrasonography, at variable gestational ages, with some cases occurring late in pregnancy, whereas others were cases booked initially in another antenatal centre and referred to our centre upon identification of hydrops. Amniocentesis was performed for fetal karyotyping in 84.6% of cases, with no chromosomal abnormalities identified in the cases studied.

There was no dropout, thus the data of all 13 cases of hydrops diagnosed antenatally or referred to our centre were used for analysis in the current study.

The majority of cases (n = 11, 84.6%) were born via lower segment caesarean section (LSCS). These included elective planned caesarean sections, and also emergency cases as indicated by maternal and fetal conditions. The mean gestation age of these newborns was 34.6 weeks (range: 31.3 to 39.2 weeks). Causes of hydrops were predominantly non-immune in origin, of which chylothorax was found to be the most common (36.4%). Chylothorax was confirmed on postnatal testing of the fluid composition and no infective aetiologies were detected. Specific testing for associated conditions such as Noonan syndrome and lymphangiogram were not performed as none of the infants were dysmorphic and the chylothorax resolved with time. Two infants with separate diagnoses of chylothorax and congenital dyserythropoietic anaemia were born to mothers who were chronic hepatitis B carriers; 3 fetuses with chylothorax and 2 with pulmonary sequestration underwent a total of 3 to 6 in-utero thoracentesis for pleural effusion. Four cases of anaemia were found in fetuses with diagnoses of rhesus isoimmunisation (n = 2), congenital dyserythropoietic anaemia (n = 1) and midgut atresia (n = 1). These fetuses with anaemia were given in-utero packed cell transfusion

Table 1. Demographic Characteristic of Infants with Fetal Hydrops Delivered

Characteristics	**n = 13**
Gender – male/female (n, %)	7/6 (53/47)
Gestational age at birth (mean, range in weeks)	34.6 +/- 2.8 (31.3 to 39.2)
Antenatal procedure (diagnostic intent)	
Amniocentesis (n, %)	11 (84.6)
Aetiology of hydrops	
Immune (n, %)	2 (15.4)
Rhesus isommunisation	2
Non-immune (n, %)	11 (84.6)
Congenital dyserythropoietic anaemia	1
Chylothorax	4
Pulmonary sequestration	2
Gut atresia (midgut, ileal, colonic)	3
Intrauterine growth restriction (due to maternal preeclampsia)	1
Birth weight (mean,+/-SD, range in g)	2572 +/- 677 (1479 to 3725)
Antenatal procedures (therapeutic intent)	9 (69.2)
Packed cell transfusions	4 (30.8%)
Thoracentesis	5 (38.5%)
Mode of delivery	
Lower section caesarean section (LSCS, %)	11 (84.6)
Normal vaginal delivery (NVD, %)	2 (15.4)
Median Apgar score at 5 minutes (range)	9 (5-9)
Mean base excess within 1st hour of life	-4.2 +/- 4.2 (-13 to 1)
Resuscitation required at birth (n, %)	3 (23.1)
Outcomes	
Death before discharge	1 (7.7)
Survived until discharge (n, %)	12 (92.3)
Survivors at 1 year of age (n, %)	11 (84.6)

(PCT) using O negative type blood at intervals of 3 to 5 weeks, with the median number of 3 PCTs given to each fetus. The remaining 4 fetuses were diagnosed with fetal hydrops late in the course of the pregnancy, and antenatal interventions could not be administered in time prior to delivery. Of these 4 fetuses, 1 had intrauterine growth restriction associated with maternal preeclampsia.

Prior to the planned date of delivery, these cases were discussed at a multidisciplinary meeting involving the neonatal and obstetrics team. Discussion was made with regards to the antenatal interventions performed, the optimal delivery time after antenatal intervention when possible and the planned neonatal resuscitation team at delivery. Regular updates were made by the obstetrics team with the neonatal team, in order to allow the neonatal team to anticipate and prepare for stabilisation of the hydropic fetus at birth. In addition, at least 2 neonatal specialists skilled in resuscitation were available during the planned delivery.

Perinatal Management

At birth, 3 neonates (23.1%) required aggressive resuscitation including cardiopulmonary resuscitation (CPR), use of adrenaline and mechanical ventilation for support. Subsequent management of the remaining neonates involved a prolonged stay in the neonatal unit, with a mean duration of 26.5 days of hospitalisation (range 7 to 69 days). Respiratory issues were a major concern for these neonates in the perinatal period. Mechanical ventilation was required in the majority of patients eventually over the course of their stay (n = 11, 84.6%), with 1 infant having severe respiratory compromise requiring escalation of support with high frequency oscillatory ventilation. Seven neonates (53.8%) required postnatal thoracocentesis; these included 4 of the 5 infants who had previously undergone antenatal thoracocentesis. All 3 infants with gut atresia received complete surgical repair and recovered from the procedure prior to discharge. Somatostatin and total parenteral nutrition was used to treat the infants with chylothorax. One neonate with chylothorax unfortunately passed away after a day in the neonatal intensive care unit despite extensive antenatal and postnatal interventions including thoracocentesis. The cause for demise was a combination of respiratory insufficiency and inability to support ventilation, and prematurity (child was born the most premature amongst the 13 cases, at 31 weeks and 3 days).

Comparison of Outcomes between Groups of Subjects With and Without Antenatal Interventions

Infants who received antenatal interventions tended to be slightly more mature, with the median gestational age at 35.0 weeks which is 1 week more than those infants who did not receive interventions antenatally ($P = 0.35$). The former group also tended to be heavier with a mean weight of 2705 g (compared with 2207 g in the latter group) ($P = 0.30$), and had better perinatal outcomes (as represented by higher Apgar score at birth and lower acidosis recorded) ($P = 0.23$) without needing aggressive resuscitation (Table 2). Nevertheless, the combined outcomes in infants of both groups remained good, with a high survival rate until discharge of 92.3% (12 out of 13 infants).

Outcomes following Discharge from Neonatal Unit

Of the 12 infants who survived until discharge, 1 infant with congenital dyserythropoietic anaemia passed away before the age of 1 year due to sepsis with liver failure. Another infant left Singapore and was lost to follow-up, but was noted to have been well during the last outpatient review in our centre. The remaining 10 infants (76.9%) were followed up until 1 year of age and were noted to have good overall outcomes, with no significant neurological impairment.

Discussion

In our study, the most common cause of fetal hydrops in our centre was Bart's hydrops. The parents were alpha-thalassaemia trait carriers. However, all of these pregnancies did not survive beyond the antenatal period due to termination of pregnancy. These pregnancies were terminated after detailed counselling by the obstetrics team with the expecting parents due to potentially life threatening maternal complications and extremely poor prognosis and invariable death of the fetus in-utero or shortly after birth.[9]

Of the remaining cases, non-immune hydrops remained the predominant cause (84.6%), with chylothorax being at the top of the list of non-immune aetiologies. Other causes

Table 2. Comparison of Characteristics of Neonates with Fetal Hydrops Requiring Antenatal Interventions and Not Requiring the Antenatal Intervention

Demographics (n = 13)	No In-Utero Intervention (n = 4)	In-Utero Intervention (n = 9)	*P* Value
Gender, males (%)	1 (25)	6 (66.7)	0.27
Mean gestational age (weeks)	33.9	35.0	0.35
Mean birth weight (g)	2274	2705	0.30
Aggressive resuscitation (%)	50.3	11.1	0.23
Median Apgar score (5 minutes)	7	9	0.68
Mean base excess (first blood gas)	-6.3	-3.3	0.20

included congenital dyserythropoietic anaemia, pulmonary sequestration, gut atresia involving the small and large bowel, and maternal preeclampsia (or Mirror syndrome). The predominance of non-immune causes for hydrops is similarly found in the Turkish review done by Takci et al,[1] which was a large retrospective review performed in recent years to investigate mortality risk factors in fetal hydrops and also in a recent Chinese retrospective study done by An X et al.[10] The encouraging results of decreasing numbers of immune-related hydrops is proof of the success of widespread efforts in recent years in identifying rhesus negative mothers early in pregnancy, and the widespread and appropriate use of anti-D immunoglobulins to reduce isoimmunisation in these rhesus negative mothers.[11,12]

We compared our findings with 2 studies done over the same period, namely that of Takci S et al,[1] who studied 62 cases of hydrops fetalis in the Turkish centre of Hacettepe University Ihsan Dogramaci Children's' Hospital from 2002 to 2011 and Ng et al[4] who studied 23 cases of non-immune fetal hydrops in our local population in Singapore from 2005 to 2010 (Tables 3 and 4). The demographics of the neonates such as gender distribution, gestational age at birth and birth weight were generally similar in the 2 published studies, and both studies focused on non-immune cases of hydrops fetalis, as in the current study.

In all 3 studies, LSCS was the predominant mode of delivery. Aggressive resuscitation was required in the majority of cases as evident from most studies with rates in our centre (23.1%). Postnatal interventions used by our centre were also common in other centres, especially in the support of the respiratory system. This is evident from the high percentage of mechanical ventilation rates required in all 3 centres, with rates of up to 84.6% shown in our study and in the study by Takci S et al.[1]

Factors affecting survival are many, with some studies attributing aetiology of the hydrops as a main prognostic factor for survival[4] while other studies suggest that the severity of disease, indicated by the number of fluid collection sites, is a main factor in predicting the risk of neonatal deaths.[5,13] Importantly, the condition of the newborn infant, including gestational age at birth is key to the prediction of survival.[4] Prematurity is known to be one of the poor prognostic factors.[5] The latter 2 causes are amenable to interventions by the neonatal and obstetrics team taking care of the mother and unborn child.

The antenatal interventions could play a role in improving survival; 69% of our cases had in-utero blood transfusions for anaemia or thoracocentesis for pleural effusions. This is comparable to 58% of antenatal interventions for the fetuses with hydrops in Takci et al's study.[1] Importantly, with these antenatal interventions used in our study, the extravascular fluid collections were reduced to decrease the risk of spontaneous preterm delivery, which is likely the contributing cause to our infants being born at more matured gestational age closer to late preterm. The long-term positive impact on fetal growth was also significant, as

Table 3. Comparison of Demographic Characteristics of Liveborns with Fetal Hydrops in the Perinatal Period with Published Studies

Demographics	NUH (n = 13)	Takci, et al (n = 62)*	Ng, et al (n = 19)†
Males (%)	53.8	46.8	68
Mean gestational age (wks)	34.6 ± 2.8	33.1 ± 2.9	33
Mean birth weight (g)	2572 ± 677	2350 ± 640	2480‡
Mode of delivery (NVD/LSCS [% LSCS])	2/11 (84.6)	9/53 (85%)	7/12 (63%)
Aggressive resuscitation at birth i.e. mechanical ventilation/CPR/drugs (%)	23.1	72.6	89
Median Apgar score (5 minutes)	9	5.7	7

CPR: Cardiopulmonary resuscitation; LSCS: Lower segment caesarean section; NUH: National University Hospital; NVD: Normal vaginal delivery
*Takci S, Gharibzadeh M, Yurdakok M, Ozyuncu O, Korkmaz A, Akcoren Z, et al. Etiology and outcome of hydrops fetalis: report of 62 cases. Pediatr Neonatol 2014;55:108-13.
†Ng ZM, Seet MJ, Erng MN, Buendia F, Chang AS, Sriram B. Nonimmune hydrops fetalis in a children's hospital: a six-year series. Singapore Med J 2013;54:487-90.
‡Median.

Table 4. Comparison of Postnatal Interventions Used

Intervention	NUH (n = 13)	Takci, et al (n = 62)*	Ng, et al (n = 19)†
Thoracentesis (%)	53.8	50.0‡	57.9
Ventilation (%)	84.6	88.7	57.9
HFOV (%)	7.7	27.1	36.8
PCT (%)	30.8	50.0	-
Mean length of stay (days)	26.5	8.5	-

HFOV: High frequency oscillatory ventilation; NUH: National University Hospital; PCT: Packed cell transfusion
*Takci S, Gharibzadeh M, Yurdakok M, Ozyuncu O, Korkmaz A, Akcoren Z, et al. Etiology and outcome of hydrops fetalis: report of 62 cases. Pediatr Neonatol 2014;55:108-13.
†Ng ZM, Seet MJ, Erng MN, Buendia F, Chang AS, Sriram B. Nonimmune hydrops fetalis in a children's hospital: a six-year series. Singapore Med J 2013;54:487-90.
‡Data provided in Table 3 of the original paper stated "thoracoparacentesis and/or blood transfusion at birth". A total tally of these 2 procedures was provided.

transfusions to correct fetal anaemia helped to reduce effect of heart failure and perpetuation of the hydropic state in the fetus, and also helps to ensure oxygen delivery to growing organs during the crucial developmental period in-utero. Thoracocentesis, on the other hand, reduces the restriction of growth of the developing fetal lungs caused by pleural effusion, minimising the outcome of lung hypoplasia in these infants. These interventions were repeated as required for the fetus since no premature labour was being triggered as a result of these procedures, proving that these essential procedures can be done safely with adequate expertise to improve the survival rates of infants with hydrops. Antenatal steroids were also administered to the mothers during pregnancy, to improve lung maturity, as preterm delivery of the fetuses with hydrops was anticipated. The overall lower rates of perinatal resuscitation required in the group who did not receive antenatal interventions compared to those who had some form of antenatal interventions for their hydrops condition (Table 2) is testament to the positive impact that antenatal interventions can make on the perinatal condition of the child, which again is pivotal in influencing the overall survival outcome. We do, however, understand that antenatal interventions performed may not be curative as evident in our study in which further thoracocentesis were required even in those infants who had already received antenatal thoracocentesis for chylothorax.

The timeliness of interventions could also have played a significant supporting role. A study by Zohra Hasnani-Samnani et al[14] looking at non-immune cases of hydrops in Qatar from 2003 to 2011 showed a high perinatal mortality rate, with 10 out of 64 births, or 16%, surviving beyond the delivery and 40% of the surviving newborns passing away within the first 6 months. Of note, 8.6% of these cases of hydrops diagnosed antenatally had been monitored closely without immediate intervention, and had eventual spontaneous resolution of symptoms. Within this group, there was an eventual demise of a fetus at 33 weeks due to intrauterine death despite the resolution of hydropic appearance on ultrasound. All in all, only 2 cases of antenatal interventions were performed.[14] This suggests that the decision on how soon the interventions ought to be performed following identification of features of hydrops on antenatal scan may influence the eventual survival outcome of these infants. In our centre, we intervene within 2 weeks of diagnosis of hydrops on antenatal ultrasound. The significantly higher rates of intervention noted in our study implies the aggressiveness and speed in instituting treatment for the fetuses at our centre, which are again important considerations for the eventual positive outcome of our hydropic fetuses.

Another possible factor that was likely to contribute to the good early survival rates was the immediate postnatal management of these infants. The median 5-minute Apgar score for our neonates with hydrops was 9. Looking at the perinatal conditions including mode of delivery and rate of aggressive resuscitation, we noted that the high rates of planned caesarean section, along with resuscitation at birth contributed hand-in-hand to provide a good immediate postnatal outcome for our neonates with hydrops. Following the immediate resuscitation, the subsequent management of the newborn was also equally important, as evident by the common use of interventions including mechanical ventilation (conventional, and high frequency oscillatory ventilation), thoracocentesis for persistent effusions to improve respiratory status and transfusions for anaemia across the 3 centres including ours. We postulate that there may be reduced necessity for postnatal interventions following the high rates of antenatal interventions that could have already positively modulated earlier issues such as pleural effusion and pulmonary hypoplasia.

Importantly, all these interventions were possible as there was close and frequent antenatal follow-up ultrasound assessment of the cases, availability of antenatal fetal interventions, and involvement of neonatologists early in the care of the cases of fetal hydrops upon diagnosis. Contribution of expertise from both the obstetrics and neonatology teams were evident from frequent discussion about the planned antenatal procedures to improve perinatal outcome, and expected condition of the fetuses at birth. The neonatologists were frequently and regularly updated on the progress of the fetus antenatally, allowing them to have a good grasp of the condition of the hydropic neonate at birth. The planning of expected perinatal procedures was possible as a result, allowing adequate nursing and medical staff in both the neonatal and obstetrics team to be available on the expected day of delivery, as well as ensuring equipment for procedures such as thoracocentesis and ventilator support were all ready for use during the same period. In addition, it was helpful for the expectant mothers who had gone through a trying pregnancy with a fetus with hydrops to meet the neonatal teams early, so that early rapport could be established. All these were possible through the combined efforts of both the obstetric and neonatal teams in our centre.

We demonstrated good long-term outcome in our centre, having 84.6% of the neonates surviving to at least 1 year of age with no neurological impairment. This is encouraging, and goes to show how good immediate outcome can have a pivoting role in determining the prognosis for the fetuses with hydrops. Antenatal interventions in-utero may contribute to this and do not negatively impact on the eventual neurological outcome of the child.[15]

Despite the encouraging rates that our retrospective study showed, a major limitation of our study was the small number of cases we gathered in these 8 years, which limited the

statistical power of our results, limiting our comparisons of the in-utero interventions given. The cases of Bart's hydrops terminated were also significant at 56.7%, which again limited the actual number of cases being studied till perinatal period. In addition, as this was a retrospective study, the interventions were not randomised to determine its efficacy. In any case, as some of these antenatal interventions are life-saving, randomisation may not be feasible due to ethical reasons.

Another limitation affecting the survival rates in non-immune hydrops is related to the variable aetiologies in each study.[16] Our study consisted of mainly cases of chylothorax, which were not the predominant cause of non-immune hydrops in the other 2 centres that Takci S et al[1] and Ng et al[2] studied about. The specific aetiologies of hydrops are an important prognostic factor for survival,[9] and hence that was a significant limiting factor in our efforts to compare the survival rates of different studies.

As such, we hope to continue to evaluate more cases of hydrops in future studies, which would capture a broader range of aetiologies, with the aim of studying the benefit of each antenatal intervention in the management of fetal hydrops, as well as to follow-up in more detail the long-term neurodevelopmental outcomes of these surviving infants. Hydrops fetalis is a serious condition, yet it can be very amenable to antenatal and perinatal interventions that can alter the outcome of a child with such a condition. Much can be done to further improve practices that can alter the mortality and morbidity rates for these fetuses.

Acknowledgement

The authors would like to thank the National University Hospital Department of Obstetrics and Gynaecology for its support and assistance in allowing the authors to review the cases in its database. They would also like to thank Dr Dimple Rajgor for her support in the editing, formatting and submission of the paper for publication.

REFERENCES

1. Takci S, Gharibzadeh M, Yurdakok M, Ozyuncu O, Korkmaz A, Akcoren Z, et al. Etiology and outcome of hydrops fetalis: report of 62 cases. Pediatr Neonatol 2014;55:108-13.
2. Fukushima K, Morokuma S, Fujita Y, Tsukimori K, Satoh S, Ochiai M, et al. Short-term and long-term outcomes of 214 cases of non-immune hydrops fetalis. Early Hum Dev 2011;87:571-5.
3. Trainor B, Tubman R. The emerging pattern of hydrops fetalis - incidence, aetiology and management. Ulster Med J 2006;75:185-6.
4. Ng ZM, Seet MJ, Erng MN, Buendia F, Chang AS, Sriram B. Nonimmune hydrops fetalis in a children's hospital: a six-year series. Singapore Med J 2013;54:487-90.
5. Huang HR, Tsay PK, Chiang MC, Lien R, Chou YH. Prognostic factors and clinical features in liveborn neonates with hydrops fetalis. Amer J Perinatol 2007;24:33-8.
6. Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA, et al. Etiology of non-immune hydrops fetalis: An update. Am J Med Genet A 2015;167:1082-8.
7. Moreno CA, Kanazawa T, Barini R, Nomura ML, Andrade KC, Gomes CP, et al. Non-immune hydrops fetalis: A prospective study of 53 cases. Am J Med Genet A 2013;161:3078-86.
8. Kooper AJ, Janssens PM, de Groot AN, Liebrand-van Sambeek ML, van den Berg CJ, Tan-Sindhunata GB, et al. Lysosomal storage diseases in non-immune hydrops fetalis pregnancies. Clin Chim Acta 2006;371:176-82.
9. Chui DH. α-Thalassemia: Hb H Disease and Hb Barts Hydrops Fetalis. Ann N Y Acad Sci 2005;1054:25-32.
10. An X, Wang J, Zhuang X, Dai J, Lu C, Li X, et al. Clinical features of neonates with hydrops fetalis. Am J Perinatol 2015;32:1231-9.
11. Stephenson T, Zuccullo J, Mohajer M. Diagnosis and management of non-immune hydrops in the newborn. Arch Dis Child 1994;70:F151-4.
12. Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. Obstet Gynecol 2008;112:164-76.
13. Yeom W, Paik ES, An JJ, Oh SY, Choi SJ, Roh CR, et al. Clinical characteristics and perinatal outcome of fetal hydrops. Obstet Gynecol Sci 2015;58:90-7.
14. Hasnani-Samnani Z, Mahmoud MI, Farid I, Al Naggar E, Ahmed B. Non-immune hydrops: Qatar experience. J Matern Fetal Neonatal Med 2013;26:449-53.
15. Harper DC, Swingle HM, Weiner CP, Bonthius DJ, Aylward GP, Widness JA. Long-term neurodevelopmental outcome and brain volume after treatment for hydrops fetalis by in utero intravascular transfusion. Am J Obstet Gynecol 2006;195:192-200.
16. Abrams M, Meredith K, Kinnard P, Clark R. Hydrops fetalis: a retrospective review of cases reported to a large national database and identification of risk factors associated with death. Pediatrics 2007;120:84-9.

Original Article

Second Malignant Neoplasms in Childhood Cancer Survivors Treated in a Tertiary Paediatric Oncology Centre

Jia Wei Lim, [1]*MBBS*, Frances SH Yeap, [1]*MBBS, MMed (Paeds), MRCPCH (UK)*, Yiong Huak Chan, [2]*B Math (Hons), PhD*, Allen EJ Yeoh, [1,3]*MBBS, MMed (Paeds)*, Thuan Chong Quah, [1,3]*MBBS, MMed (Paeds)*, Poh Lin Tan, [1,3]*MBBS, MMed (Paeds), FAMS (S'pore)*

Abstract

Introduction: One of the most feared complications of childhood cancer treatment is second malignant neoplasms (SMNs). This study evaluates the incidence, risk factors and outcomes of SMNs in a tertiary paediatric oncology centre in Singapore. Materials and Methods: A retrospective review was conducted on patients diagnosed with childhood cancer under age 21 and treated at the National University Hospital, Singapore, from January 1990 to 15 April 2012. Case records of patients with SMNs were reviewed. Results: We identified 1124 cases of childhood cancers with a median follow-up of 3.49 (0 to 24.06) years. The most common primary malignancies were leukaemia (47.1%), central nervous system tumours (11.7%) and lymphoma (9.8%). Fifteen cases developed SMNs, most commonly acute myeloid leukaemia/myelodysplastic syndrome (n = 7). Median interval between the first and second malignancy was 3.41 (0.24 to 18.30) years. Overall 20-year cumulative incidence of SMNs was 5.3% (95% CI, 0.2% to 10.4%). The 15-year cumulative incidence of SMNs following acute lymphoblastic leukaemia was 4.4% (95% CI, 0% to 8.9%), significantly lower than the risk after osteosarcoma of 14.2% (95% CI, 0.7% to 27.7%) within 5 years (P <0.0005). Overall 5-year survival for SMNs was lower than that of primary malignancies. Conclusion: This study identified factors explaining the epidemiology of SMNs described, and found topoisomerase II inhibitor use to be a likely risk factor in our cohort. Modifications have already been made to our existing therapeutic protocols in osteosarcoma treatment. We also recognised the importance of other risk management strategies, including regular long-term surveillance and early intervention for detected SMNs, to improve outcomes of high risk patients.

Ann Acad Med Singapore 2017;46:11-9

Key words: Late effects, Long-term cancer survivors, Topoisomerase II inhibitor

Introduction

Second malignant neoplasms (SMNs) have been recognised as a late complication of oncologic therapy since the 1970s,[1] as advancements in diagnosis and treatment of childhood cancer led to significant improvements in survival. SMNs are 3- to 7-fold as common in childhood cancer survivors as compared to the general population[2-5] and represent a significant cause of morbidity and mortality in childhood cancer survivors, rising from 4% of mortalities at 5 to 10 years to 33% at 30 years after diagnosis.[6] It is vital to identify and minimise patient exposure to the risk factors of SMN whilst not compromising cure rates.

Identified risk factors for SMNs involve both host- and treatment-related aspects, including younger age at diagnosis, underlying genetic predisposition, radiotherapy and chemotherapy.[7,8] Secondary solid tumours have been associated with prior radiotherapy with a dose-dependent relationship, and are typically found within the radiation field following a latency of 10 years. On the other hand, the risk of haematological SMNs and myelodysplastic syndrome (MDS) is more strongly associated with chemotherapeutic agents. Specific characteristics have also been linked with certain chemotherapeutic agents, facilitating identification of risk factors in therapeutic protocols.[9] Acute myeloid

[1]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore
[2]Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Address for Correspondence: Dr Tan Poh Lin, Department of Paediatrics, NUHS Tower Block Level 12, 1E Kent Ridge Road, Singapore 119228.
Email: poh_lin_tan@nuhs.edu.sg

leukaemia (AML) related to alkylating agents and radiation are commonly of M1, M2, M6 and M7 phenotypes, and feature a relatively longer latency of 4 to 6 years with a myelodysplastic phase prior to leukaemic transformation. Deletions of all or part of chromosomes 5 and 7 are also typical. In contrast, secondary AML following treatment with topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins) are often of M4 and M5 subtypes and occur within a short median latency of 24 to 33 months without a myelodysplastic phase. They are also associated with translocations to 11q23 (involving the mixed-lineage leukaemia [MLL] gene) and 21q22 (RUNX1). Other chromosomal abnormalities such as inv(16), t(15;17) and involvement of 11p15 (NUP98) have been linked with prior combination therapy with alkylating agents and topoisomerase II inhibitors. Regardless of aetiology, therapy-related leukaemias carry a poor prognosis.[9,10] Understanding these associations enables the implementation of strategies such as modified regimens and surveillance protocols[11] to improve long-term outcomes for patients at risk.

While studies have been undertaken to characterise SMNs in regions such as Europe and North America, this is the first study to investigate SMNs within Singapore and Southeast Asia. We present findings of a retrospective review to evaluate the incidence, risk factors and outcomes of SMNs in long-term cancer survivors in a tertiary paediatric oncology centre in Singapore.

Materials and Methods

Patients and Methods

The Singapore Childhood Cancer Registry (SCCR) is a multi-institutional childhood cancer registry that studies the epidemiology of childhood cancers within our multiracial Asian population.[12] All childhood cancers were notified to the SCCR by 2 main institutions: KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). These 2 institutions report more than 92% of childhood cancer cases in Singapore, with the remaining reported by private institutions. All cases captured are counterchecked with the Singapore Cancer Registry and the National Birth and Death Registry to ensure data accuracy.

All childhood cancer patients with primary malignancy or SMN, diagnosed under the age of 21 and treated at NUH between January 1990 and 15 April 2012, were included in this study. A list of these patients was generated from the SCCR, including data regarding their diagnoses and outcomes. Duration of follow-up was defined as the period from the date of diagnosis of primary neoplasm to the date of death or last known follow-up accurate up to the last review on 15 April 2014. Clinical records of all patients who had developed SMNs were individually reviewed. Primary cancers and SMNs were classified according to the International Classification of Childhood Cancer (ICCC).[13] SMN is defined as a histologically distinct cancer that develops after the first cancer. Non-melanoma skin cancers were also included. For patients who developed SMNs, pathological reports were reviewed for inclusion into the study and treatment-related data of the primary malignancy, relapses and conditioning for stem cell transplantations up to the event of SMNs were also collected.

Statistical Analysis

Cumulative incidence of SMN, overall survival and survival following specific neoplasms were calculated by Kaplan-Meier method with SPSS version 20.0 (SPSS Inc., USA). Ninety-five percent confidence interval (CI) was calculated from the standard error. Patients who were treated in other oncology centres for their primary cancer and referred to our centre for the management of SMNs were excluded from cumulative incidence and hazard ratio calculations but included in survival analysis. Hazard ratios were determined via a Cox regression model. Survival after SMN was defined as time from diagnosis of SMN to death from any cause, or until the last known follow-up.

Results

A total of 1124 patients were included in the study, including 4 who presented to the institution during their SMN. Median duration of follow-up was 3.49 (0 to 24.06) years and 857 patients were alive at the time of last data review. Of the 1124 patients, 670 (59.6%) patients were male and 454 (40.4%) female. Five-year overall survival was 73.8% (95% CI, 70.9 to 76.7%). Median age at diagnosis of primary malignancy was 5.43 (0 to 20.71) years. The most common primary malignancies were leukaemia (47.1%), central nervous system (CNS) tumours (11.7%) and lymphoma (9.8%); 31.4% were other malignancies. Table 1 shows the distribution of primary and second malignancies.

Second Malignant Neoplasms

Of the 1124 patients in the study, 15 developed SMNs, of whom 4 presented to our institution only during their SMN. It was made known to us that another patient had developed a benign second neoplasm (benign meningioma) 12.36 years after receiving chemotherapy and radiotherapy for medulloblastoma. In patients with SMN, the median age of diagnosis for primary and SMN were 6.24 (0.13 to 16.48) years and 14.56 (2.71 to 18.43) years, respectively, with a median interval period of 3.41 (0.24 to 18.30) years. The proportion of childhood cancer survivors that developed SMNs were 1.5% and 1.1% for males and

Table 1. Characteristics of Childhood Cancer Survivors (n = 1124)

Characteristics	No. of Patients (n, %)	Cases with SMN (n)
Vital status		
Alive	857 (76.2)	7
Dead	267 (23.8)	8
Gender		
Male	670 (59.6)	10
Female	454 (40.4)	5
Primary diagnosis*		
Leukaemia	529 (47.1)	7
CNS tumours	132 (11.7)	0
Lymphoma	110 (9.8)	3
Bone tumours	79 (7.0)	4
Neuroblastoma	65 (5.8)	0
Germ cell tumours	56 (5.0)	0
Soft tissue sarcomas	43 (3.8)	0
Retinoblastoma	39 (3.5)	0
Renal tumours	37 (3.3)	0
Hepatic tumours	26 (2.3)	0
Carcinomas	5 (0.4)	1
Others	3 (0.3)	0

CNS: Central nervous system; SMN: Second malignant neoplasms
*Diagnoses were classified according to International Classification of Childhood Cancer (ICCC)

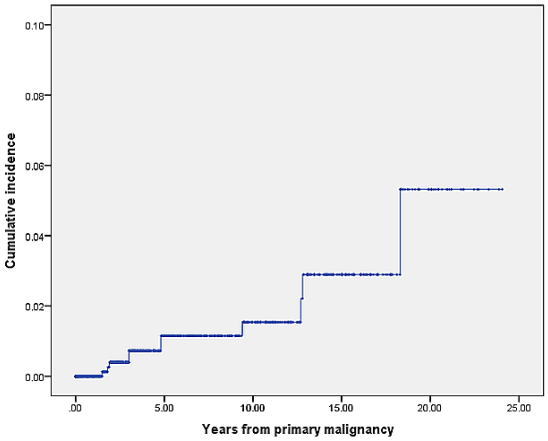

Fig. 1. Cumulative incidence of second malignant neoplasms in our centre.

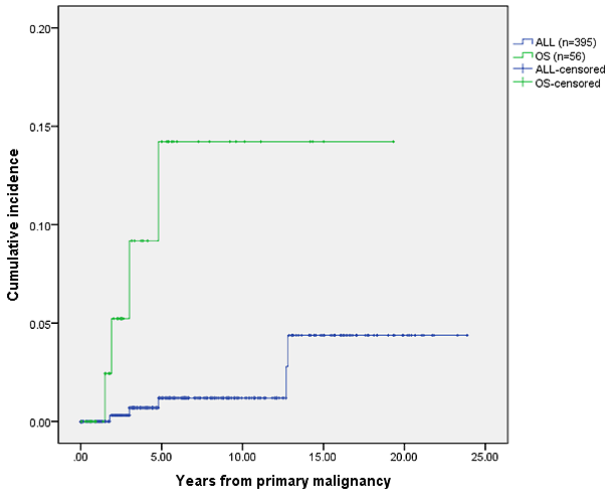

Fig. 2. Cumulative incidence of second malignant neoplasms in patients with acute lymphoblastic leukaemia and osteosarcoma.
ALL: Acute lymphoblastic leukaemia; OS: Osteosarcoma

females, respectively. The most common SMN was acute leukaemia (n = 11), followed by 2 cases of osteosarcoma and 1 each of atypical meningioma and peripheral T-cell lymphoma. Of the 11 cases of secondary leukaemia, 7 were AML/MDS, 2 were acute lymphoblastic leukaemia (ALL) and 2 were mixed phenotype acute leukaemia (MPAL). Excluding 4 patients who were referred to our centre during their SMN, the 10-year and 20-year cumulative incidence for development of SMN were 1.5% (95% CI, 0.3% to 2.7%) and 5.3% (95% CI, 0.2% to 10.4%), respectively (Fig. 1). The 15-year cumulative incidence of SMNs following ALL was 4.4% (95% CI, 0% to 8.9%), while the cumulative risk after primary osteosarcoma was significantly higher, reaching 14.2% (95% CI, 0.7% to 27.7%) within 5 years (P <0.0005) (Fig. 2). The hazard ratio of developing SMN in patients with ALL compared to patients with other tumour types (excluding osteosarcoma) was 3.22 (95% CI, 0.625 to 16.61), whereas that of patients with osteosarcoma was 30.14 (95% CI, 5.48 to 165.71).

Table 2 summarises the clinical characteristics of patients who developed SMNs, including the type of primary and second malignancies, treatment received, chemotherapy regimen, latency and outcomes. Two patients had a positive family history of cancer in their second-degree relative.

In view of late effects associated with radiation in childhood, only a limited number of patients in our programme received radiation as part of primary therapy. Of the patients with SMNs, 2 patients were exposed to radiotherapy and both had ALL – 1 received cranial radiation in combination with chemotherapy for ALL relapse (CNS and bone marrow), while the other underwent total body irradiation as part of the preparative regimen for allogeneic stem cell transplant (SCT). Both patients subsequently developed haematological malignancies (AML and MPAL, respectively). Another patient with mixed gonadal

Table 2. Clinical Characteristics of Patients with SMN

No.	Gender	Primary Neoplasm	Age at Diagnosis	Treatment of Primary Neoplasm*	Chemotherapy	SMN	Age at Diagnosis	Latency	Treatment of Second Neoplasm	Outcome
1	M	ALL	6.5	Chemotherapy (MASPORE ALL 2010 HR), 2 x Allogenic SCT (with TBI)	6-MP, 6-TG, ATG, Ara-C, CPM, Clo, Dasatinib, Dexa, DNR, Flu, Imatinib, L-asp, MTX, Pred, VCR, VP-16	MPAL	9.5	3.0	Chemotherapy + adoptive cell therapy	DOD
2	F	ALL	4.5	Chemotherapy (NUH 1996)	6-MP, 6-TG, Ara-C, CPM, Dexa, DNR, L-asp, MTX, Pred, VCR, VM-26	MPAL	17.2	12.7	Chemotherapy + allogenic SCT (with TBI)	A-NED
3‡	M	ALL	3.5	Chemotherapy (NUH 1996)	6-MP, 6-TG, Ara-C, CPM, Dexa, DNR, L-asp, MTX, Pred, VCR, VM-26	AML	16.3	12.8	Chemotherapy + allogenic SCT	DOTC
4	M	ALL	7.5	Chemotherapy (MASPORE ALL 2002 SR & 2003 HR, FLAG) + RT	6-MP, 6-TG, Ara-C, CPM, Dexa, DNR, DXR, Flu, L-asp, MTX, Pred, VCR	AML	12.3	4.8	Allogenic SCT (with TBI)	AWD
5	M	ALL	6.2	Chemotherapy (MASPORE ALL 2002/2010 IR)	6-MP, 6-TG, Ara-C, CPM, Dexa, DXR, L-asp, MTX, Pred, VCR	NHL	8.1	1.8	Chemotherapy	DOD
6§	F	Disseminated LCH	0.4	Chemotherapy (LCH II, LCH-S-98)	2-CdA, 6-MP, CsA, MTX, Pred, VBL, VP-16	ALL	18.4	18.0	Chemotherapy	DOTC
7†	M	Burkitt's lymphoma	5.1	Chemotherapy (Lyon 903)	Ara-C, CPM, DXR, MTX, Pred, VCR, VP-16	Atypical meningioma	14.5	9.4	Surgery	A-NED
8	M	Osteosarcoma	12.7	Chemotherapy (OS protocol with MTP) + surgery	CDDP, DXR, MTP, MTX	MDS	14.6	1.9	Supportive care	AWD
9	M	Osteosarcoma	9.1	Chemotherapy (NUH protocol A) + surgery	CDDP, DXR, IFO, MTX, VP-16	AML	12.1	3.0	Chemotherapy + allogenic SCT (with TBI) + adoptive cell therapy	AWD
10	M	Osteosarcoma	12.7	Chemotherapy (NUH protocol A) + surgery	CDDP, DXR, IFO, MTX, VP-16	AML	17.5	4.8	Chemotherapy	DOD
11†	F	Osteosarcoma	15.4	Chemotherapy (NUH protocol B) + surgery	CDDP, DXR, IFO, MTX, VP-16	AML	16.9	1.5	Chemotherapy + allogenic SCT (with TBI)	DOD

2-CdA: Cladribine; 6-MP: Mercaptopurine; 6-TG: Thioguanine; ABVD: Adriamycin, bleomycin, vinblastine and dacarbazine; ALL: Acute lymphoblastic leukaemia; AML: Acute myeloblastic leukaemia; A-NED: Alive with no evidence of disease; Ara-C: Cytarabine; ATG: Anti-thymocyte globulin; AWD: Alive with disease; Bleo: Bleomycin; CCNU: Lomustine; Clo: Clofarabine; CPM: Cyclophosphamide; CsA: Cyclosporine A; Dexa: Dexamethasone; DNR: Daunorubicin; DOD: Died of disease; DOTC: Died of treatment complication; DXR: Doxorubicin; F: Female; FLAG: Fludarabine, cytarabine and granulocyte colony-stimulating factor; Flu: Fludarabine; HR: High risk; IFO: Ifosfamide; IR: Intermediate risk; L-asp: L-asparaginase; LCH: Langerhans cell histiocytosis; M: Male; MASPORE ALL: Singapore-Malaysia acute lymphoblastic leukaemia treatment protocol; MPAL: Mixed phenotype acute leukaemia; MRC: Medical Research Council; MTP: Muramyl tripeptide; MTX: Methotrexate; NHL: Non-Hodgkin lymphoma; NUH: National University Hospital; OS: Osteosarcoma; Pred: Prednisolone; RT: Radiotherapy; SCT: Stem cell transplant; SMN: second malignant neoplasm; SR: Standard risk; TBI: Total body irradiation; VBL: Vinblastine; VCR: Vincristine; VM-26: Teniposide; VP-16: Etoposide

*Chemotherapeutic protocols are reflected in brackets.

†Patients with family history of cancer in 2nd degree relatives.

‡Patients with a third malignant neoplasm (not reflected in table).

§Patient was treated at multiple centres for her primary neoplasm.

||Patients who presented during their SMN.

Table 2. Clinical Characteristics of Patients with SMN (Con't)

No.	Gender	Primary Neoplasm	Age at Diagnosis	Treatment of Primary Neoplasm*	Chemotherapy	SMN	Age at Diagnosis	Latency	Treatment of Second Neoplasm	Outcome
12‡,‖	F	Thyroid carcinoma	16.5	Surgery + radioiodine	-	Osteosarcoma	16.7	0.2	Chemotherapy + surgery	DOD
13‖	F	ALL	5.9	Chemotherapy	6-MP, 6-TG, Ara-C, CPM, Dexa, DXR, L-asp, MTX, Pred, VCR	AML	9.3	3.4	Chemotherapy + allogenic SCT	A-NED
14‖	M	AML	0.8	Chemotherapy (MRC 15)	Ara-C, DNR, Flu, Mitoxantrone, VP-16	ALL	2.7	1.9	Chemotherapy	DOTC
15‖	M	Hodgkin's lymphoma	3.0	Chemotherapy (ABVD)	Bleo, Dacarbazine, DXR, VBL	Osteosarcoma	15.4	12.4	Chemotherapy + surgery	A-NED

2-CdA: Cladribine; 6-MP: Mercaptopurine; 6-TG: Thioguanine; ABVD: Adriamycin, bleomycin, vinblastine and dacarbazine; ALL: Acute lymphoblastic leukaemia; AML: Acute myeloblastic leukaemia; A-NED: Alive with no evidence of disease; Ara-C: Cytarabine; ATG: Anti-thymocyte globulin; AWD: Alive with disease; Bleo: Bleomycin; CCNU: Lomustine; Clo: Clofarabine; CPM: Cyclophosphamide; CsA: Cyclosporine A; Dexa: Dexamethasone; DNR: Daunorubicin; DOD: Died of disease; DOTC: Died of treatment complication; DXR: Doxorubicin; F: Female; FLAG: Fludarabine, cytarabine and granulocyte colony-stimulating factor; Flu: Fludarabine; HR: High risk; IFO: Ifosfamide; IR: Intermediate risk; L-asp: L-asparaginase; LCH: Langerhans cell histiocytosis; M: Male; MASPORE ALL: Singapore-Malaysia acute lymphoblastic leukaemia treatment protocol; MPAL: Mixed phenotype acute leukaemia; MRC: Medical Research Council; MTP: Muramyl tripeptide; MTX: Methotrexate; NHL: Non-Hodgkin lymphoma; NUH: National University Hospital; OS: Osteosarcoma; Pred: Prednisolone; RT: Radiotherapy; SCT: Stem cell transplant; SMN: second malignant neoplasm; SR: Standard risk; TBI: Total body irradiation; VBL: Vinblastine; VCR: Vincristine; VM-26: Teniposide; VP-16: Etoposide

*Chemotherapeutic protocols are reflected in brackets.

†Patients with family history of cancer in 2nd degree relatives.

‡Patients with a third malignant neoplasm (not reflected in table).

§Patient was treated at multiple centres for her primary neoplasm.

‖Patients who presented during their SMN.

dysgenesis (45XO/46XY mosaic) received radioiodine for thyroid follicular cancer and developed osteosarcoma with a short latency of 0.2 years.

There were 2 other cases of solid SMNs in our cohort – osteosarcoma and atypical meningioma, occurring after Hodgkin's and Burkitt's lymphoma, respectively. Both lymphomas were treated with chemotherapy only.

Of the 12 patients who developed haematological SMNs (leukaemia and lymphoma), all but 2 had cytogenetic abnormalities (Table 3). Five of these cases (patients 3, 4, 8, 9 and 11) who were exposed to topoisomerase II inhibitor had involvement of 11q23, 11p15 or 21q22. Chromosome 7 deletion was noted in patient 14 but details of the chemotherapy received are not known to us. Patient 12 also displayed abnormal cytogenetics in her third malignancy of chronic myelomonocytic leukaemia (CMML) (not reflected in Table 3) involving 11q23 after receiving topoisomerase II inhibitors for her SMN.

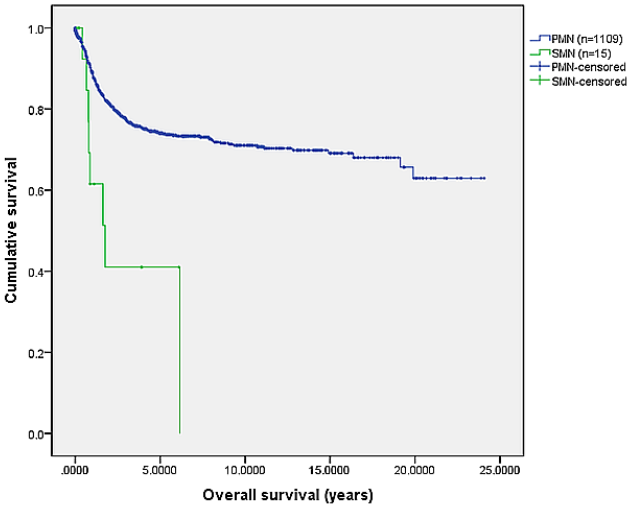

Fig. 3. Overall survival of patients with primary and secondary malignant neoplasms.
PMN: Primary malignant neoplasm, SMN: Secondary malignant neoplasm

Third Malignant Neoplasms

Following treatment for SMN, 2 patients developed a third malignancy. Patient 3 underwent treatment for secondary AML, including SCT which was complicated by chronic oral graft versus host disease, and developed squamous cell carcinoma (SCC) of the tongue 5.34 years after the SMN. He received standard treatment for the SCC. Patient 12 had CMML 1.28 years following diagnosis of secondary osteosarcoma and received metronomic therapy.

Outcome

Of all 15 patients with SMNs, 5 died of disease progression and 2 of treatment complications within 2 years of diagnosis of SMN/third malignancy. Patient 3 survived 6.16 years after AML (0.82 years after SCC) before succumbing to treatment complications of his third malignancy, while patient 12 survived 1.76 years following osteosarcoma (0.48 years after CMML) before succumbing to the disease. Of the 7 SMN survivors, 4 are alive with no evidence of disease while 3 have residual disease. Overall 5-year survival rate for SMNs was 41.0% (95% CI, 11.8% to 70.2%), significantly lower compared to 74% (95% CI, 71.1% to 76.9%) for primary malignancies (P <0.0005) (Fig. 3).

Discussion

Several large scale cohort studies have provided vital information on epidemiology, risk factors and prognosis of patients with SMNs. The Nordic study (1943 to 2005) involving a population-based cohort of childhood cancer patients reported a 9% cumulative risk for SMNs at an attained age of 60,[5] with leukaemia (26%), CNS neoplasm (23%), and lymphoma (13%) being the main primary malignancies. Similarly, the United States (US) Childhood Cancer Survivor Study (CCSS) (1970 to 1986) studied 5-year survivors of childhood cancer and reported a cumulative incidence of SMN of 3.2% at 20 years after diagnosis, with the main SMNs being breast cancer (22%), thyroid cancer (14%) and CNS tumours (11%).[4] Beyond the West, a tertiary paediatric oncology centre in Hong Kong studied 1374 cases of childhood cancer treated from 1984 to 2009, with a 20-year cumulative incidence of 2.9%.[14] The most common primary malignancies were leukaemia (44.6%), CNS (12.9%) and bone (8.2%) tumours. Of the 16 patients who developed SMNs, the most frequent SMNs were acute leukaemia/MDS (n = 6) and CNS tumour (n = 4).

The epidemiology of primary malignancies and SMNs in our centre-based cohort was found to be more similar to the Hong Kong study. The proportion of haematological SMN (leukaemias and lymphomas) in our cohort was 56.9%, comparable to Hong Kong (51%) and the US (54.5%), but substantially higher than the Nordic cohort (39.9%). The most common SMN in both our cohort and in Hong Kong was leukaemia, while solid tumours were predominant across the Nordic, US, British and Canadian cohorts.[3-5,15] The pattern in SMN epidemiology is likely related to the epidemiology of primary malignancies and their respective treatments. In the Nordic and CCSS groups, more than a third (36% and 34%, respectively) of the primary malignancies were CNS tumours and lymphoma, where the mainstay of treatment is radiation-based. In contrast, haematological SMN is more related to exposure to specific chemotherapeutic agents for primary malignancies such as leukaemia and osteosarcoma

Table 3. Specific Chemotherapeutic Agents Received and Cytogenetic Profile of Patients with Secondary Acute Leukaemia or Lymphoma

No.	Primary Malignancy	Alkylating Agents		Platinum Compounds	Anthracyclines	Epipodophyllotoxins		SMN	Latency	Cytogenetics
		CPM (mg/m²)	IFO (mg/m²)	CDDP (mg/m²)	DXR/DNR* (mg/m²)	VP-16 (mg/m²)	VM-26 (mg/m²)			
1	ALL	8595.5	-	-	83.3	500	-	MPAL	3.0	Complex karyotype§
2	ALL	1200	-	-	62.5	-	600	MPAL	12.7	46,XX,t(2;14)(p11.2;q11.2)
3	ALL	1200	-	-	62.5	-	600	AML	12.8	46,XY,t(8;21)(q22;q22)/46,XY
4	ALL	6000	-	-	353.3	-	-	AML	4.8	46,XY,t(9;11)(p22;q23)/46,XY
5	ALL	-	-	-	-	-	-	NHL	1.8	46, XY
6†	Histiocytosis X	-	-	-	-	-	-	ALL	18.0	46-47,XX,der(7)t(7;12)(q32;q13), del(9)(p22)[12], ?inv(11)(q13q23),+14[6][cp15]/46,XX[5]
8	Osteosarcoma	-	-	480	450	-	-	MDS	1.9	46,XY,t(1;11)(q23;p15)
9	Osteosarcoma	-	36000	480	450	5000	-	AML	3.0	46,XY,del(16)(p13.1),del(16)(q22),+(17)(q25),+(21)(q22)/46,XY
10	Osteosarcoma	-	55220	360	446.9	1500	-	AML	4.8	47XY,+8,del(9)(q13q22) /48,idem,+del(9)/46XY
11	Osteosarcoma	-	44500	480	450	1500	-	AML	1.5	46XX,t(9;11)(p22;q23)
13‡	ALL	-	-	-	-	-	-	AML	3.4	46,XX
14‡	AML	-	-	-	-	-	-	ALL	1.9	46,XY,del(7)(q22q32)/46,XY

ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; CDDP: Cisplatin; CPM: Cyclophosphamide; DNR: Daunorubicin; DXR: Doxorubicin; IFO: Ifosfamide; MDS: Myelodysplastic; MPAL: Mixed phenotype acute leukaemia; NHL: Non-Hodgkin lymphoma; SMN: Second malignant neoplasm; VM-26: Teniposide; VP-16: Etoposide

*Daunorubicin converted into doxorubicin isotoxic dose using the formula: daunorubicin cumulative dose x 0.833 = doxorubicin isotoxic dose.

†Patient was treated at multiple centres for her primary neoplasm.

‡Patients who presented during their SMN.

§Significant abnormalities include del(5q), del(7q), del(9q), +(3q), +(8q) and +(17p).

and has a shorter latency than solid tumours. They may therefore represent a larger proportion of SMNs in studies with relatively short follow-up periods, such as in our study and Hong Kong.

The 20-year cumulative incidence of SMN was 5.3% in our cohort (January 1990 to April 2012), higher than that described in Western cohorts and in Hong Kong (2.9%) (May 1984 to June 2009). It is worth noting that with the exception of the population-based Nordic cohort, the other Western cohorts discussed above examined 5-year survivors. It has been observed that over 40% of SMNs occur within the first 5 years after diagnosis, and these were predominantly haematological SMNs.[16] Studies that restricted participants to 5-year survivors may be underestimating the true risk of SMNs, especially secondary haematological malignancies with relatively short latency periods. Additionally, the Hong Kong study focused on patients who were treated 5 to 10 years earlier as compared to our cohort and were likely exposed to different types/intensities of treatments. Recent intensive therapeutic protocols may have improved cure rates of primary malignancies, increasing the incidence of SMNs as childhood cancer survivors live longer.

Most SMNs in our cohort occurred after ALL or osteosarcoma, with an increased risk associated with osteosarcoma. The 15-year cumulative risk of SMNs after ALL in our cohort is 4.4%, comparable to other studies describing overall risks from 3.3% at 15 years[17] to 5.37% at 20 years[18] and 5.2% at 25 years.[4] In contrast, the 5-year cumulative incidence of SMN after osteosarcoma is 14.1%, substantially higher than a larger US centre that reported a 10-year cumulative incidence of 3.1%.[19] The high incidence of SMN in our patients with osteosarcoma who were treated on a modified regimen derived from the same US centre, is of concern and warrants further study for risk factors that might be specific to our population.

Balanced chromosomal rearrangements are the hallmark of therapy-related leukaemia in patients treated with alkylating agents and topoisomerase II inhibitors. An analysis of the haematological SMNs in our cohort revealed cytogenetic features consistent with therapy-related malignancies. Topoisomerase II inhibitor use was a consistent feature and a likely major risk factor in our cohort. Since 2000, the epipodophyllotoxin teniposide has been removed from our treatment regimens for ALL. We have also revised our osteosarcoma protocols such that patients with metastatic osteosarcoma are no longer treated with additional ifosfamide and etoposide in view of recent data showing increased toxicities without improvement in outcomes.[20]

Childhood cancer survivors continue to have increased overall mortality over the general population despite treatment.[6,21-23] Not unexpectedly, we found that overall survival of patients with SMNs was much poorer than in primary malignancies, with fewer than half surviving beyond 2 years. Our experience concurs with others that secondary AML carries poor prognosis and is often resistant to treatment, including SCT.[10]

This study is limited by several factors. The relatively short median follow-up of 3.49 years is just above the median latency for SMN development (3.41 years), hence SMNs that develop over time may be missed, underestimating the true risk of SMNs. Secondly, our data only captures patients from one centre and may not be representative of the overall population. Thirdly, the registry does not reflect other useful information such as treatment regimen, toxicities, complications and prevalence of hereditary cancer syndromes. Benign neoplasms may therefore be under-reported. Furthermore, the general weaknesses inherent to registry data research, including reporting delays, incomplete reporting and loss to follow-up, limits data accuracy. Nonetheless, reviewing clinical records for patients with SMNs ensured data accuracy in these patients. Future collaboration in a multicentre study may provide a larger study population.

Conclusion

This study demonstrated differences in the epidemiology of primary and SMNs, with haematological malignancies constituting the majority in our cohort as compared to solid tumours in the West. A significant risk of SMNs in patients with ALL and osteosarcoma was found, with SMN incidence in patients with osteosarcoma being particularly elevated compared to other centres. With topoisomerase II inhibitor use identified as a likely risk factor, modifications have already been made to our existing therapeutic protocols in osteosarcoma treatment. Other risk management strategies, including regular long-term surveillance, with early intervention for detected SMNs may serve to improve outcomes of patients at risk of SMN.

Acknowledgement

The authors would like to thank Miss Chua Hsin Chieh for her administrative support through the course of this research. They would also like to thank the team of doctors and nurses at the Khoo Teck Puat-National University Children's Medical Institute Paediatric Haematology-Oncology Unit for their dedication and care for patients with childhood cancer.

REFERENCES

1. Wong FL, Boice JD Jr, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 1997;278:1262-7.
2. Jenkinson HC, Hawkins MM, Stiller CA, Winter DL, Marsden HB, Stevens MC. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. Br J Cancer 2004;91:1905-10.
3. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Phillips N, McBride ML. Risk of a second malignant neoplasm among 5-year survivors of cancer in childhood and adolescence in British Columbia, Canada. Pediatr Blood Cancer 2007;48:453-9.
4. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27:2356-62.
5. Olsen JH, Moller T, Anderson H, Langmark F, Sankila R, Tryggvadottir L, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 2009;101:806-13.
6. Garwicz S, Anderson H, Olsen JH, Falck Winther J, Sankila R, Langmark F, et al. Late and very late mortality in 5-year survivors of childhood cancer: changing pattern over four decades—experience from the Nordic countries. Int J Cancer 2012;131:1659-66.
7. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. Nat Rev Cancer 2002;2:124-32.
8. Choi DK, Helenowski I, Hijiya N. Secondary malignancies in pediatric cancer survivors: perspectives and review of the literature. Int J Cancer 2014;135:1764-73.
9. Ng A, Taylor GM, Eden OB. Treatment-related leukaemia–a clinical and scientific challenge. Cancer Treat Rev 2000;26:377-91.
10. Sandler ES, Friedman DJ, Mustafa MM, Winick NJ, Bowman WP, Buchanan GR. Treatment of children with epipodophyllotoxin-induced secondary acute myeloid leukemia. Cancer 1997;79:1049-54.
11. Hudson MM, Mulrooney DA, Bowers DC, Sklar CA, Green DM, Donaldson SS, et al. High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. J Clin Oncol 2009;27:2405-14.
12. Aung L, Khyne T, Yeoh AE, Quah TC, Tan AM. A report from the Singapore Childhood Cancer Survivor Study (SG-CCSS): a multi-institutional collaborative study on long-term survivors of childhood cancer, initial analysis reporting for the SG-CCSS. Ann Acad Med Singapore 2009;38:684-9.
13. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer 2005;103:1457-67.
14. Sun WF, Cheng FW, Lee V, Leung WK, Shing MK, Yuen PM, et al. Second malignant neoplasms in childhood cancer survivors in a tertiary paediatric oncology centre in Hong Kong, China. Chin Med J (Engl) 2011;124:3686-92.
15. Reulen RC, Frobisher C, Winter DL, Kelly J, Lancashire ER, Stiller CA, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 2011;305:2311-9.
16. Pole JD, Gu LY, Kirsh V, Greenberg ML, Nathan PC. Subsequent malignant neoplasms in a population-based cohort of pediatric cancer patients: a focus on the first 5 years. Cancer Epidemiol Biomarkers Prev 2015;24:1585-92.
17. Loning L, Zimmermann M, Reiter A, Kaatsch P, Henze G, Riehm H, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 2000;95:2770-5.
18. Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA 2007;297:1207-15.
19. Aung L, Gorlick RG, Shi W, Thaler H, Shorter NA, Healey JH, et al. Second malignant neoplasms in long-term survivors of osteosarcoma: Memorial Sloan-Kettering Cancer Center Experience. Cancer 2002;95:1728-34.
20. Marina N, Smeland S, Bielack SS, Bernstein M, Jovic G, Hook JM, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. Lancet Oncol 2016;17:1396-408.
21. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2008;100:1368-79.
22. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. Pediatr Blood Cancer 2007;48:460-7.
23. Reulen RC, Winter DL, Frobisher C, Lancashire ER, Stiller CA, Jenney ME, et al. Long-term cause-specific mortality among survivors of childhood cancer. JAMA 2010;304:172-9.

Original Article

Gender Differences in Knowledge, Attitudes and Practices towards Cardiovascular Disease and its Treatment among Asian Patients

Tong Shen,[*1], Tse Yean Teo,[*1], Jonathan JL Yap, [2]*MBBS, MRCP*, Khung Keong Yeo,[2,3]*MBBS, ABIM (Int Med, US), ABIM (Cardiology, US)*

Abstract

Introduction: Knowledge, attitudes and practices (KAP) impact on cardiac disease outcomes, with noted cultural and gender differences. In this Asian cohort, we aimed to analyse the KAP of patients towards cardiac diseases and pertinent factors that influence such behaviour, focusing on gender differences. Materials and Methods: A cross-sectional survey was performed among consecutive outpatients from a cardiac clinic over 2 months in 2014. Results: Of 1406 patients approached, 1000 (71.1%) responded (mean age 57.0 ± 12.7 years, 713 [71.3%] males). There was significant correlation between knowledge and attitude scores (r = 0.224, *P* <0.001), and knowledge and practice scores (r = 0.114, *P* <0.001). There was no correlation between attitude and practice scores. Multivariate predictors of higher knowledge scores included female sex, higher education, higher attitude and practice scores and prior coronary artery disease. Multivariate predictors of higher attitude scores included higher education, higher knowledge scores and non-Indian ethnicity. Multivariate predictors of higher practice scores included male sex, Indian ethnicity, older age, higher knowledge score and hypertension. Males had lower knowledge scores (85.8 ± 8.0% vs 88.0 ± 8.2%, *P* <0.001), lower attitude scores (91.4 ± 9.4% vs 93.2 ± 8.3%, *P* = 0.005) and higher practice scores (58.4 ± 18.7% vs 55.1 ± 19.3%, *P* = 0.013) than females. Conclusion: In our Asian cohort, knowledge of cardiovascular health plays a significant role in influencing attitudes and practices. There exists significant gender differences in KAP. Adopting gender-specific strategies for future public health campaigns could address the above gender differences.

Ann Acad Med Singapore 2017;46:20-8

Key words: Health behaviour, Health promotion, Public health

Introduction

Cardiac disease (CD) imposes a significant health burden worldwide in both men and women.[1] Various factors such as demographics and socioeconomic status have been shown to influence knowledge, attitudes and practices (KAPs) towards CD.[2-4] The understanding of KAP and its predictors are important as these have been shown to affect cardiovascular outcomes.[5] Associations between lower knowledge scores and higher risk of stroke and myocardial infarction have been reported.[6]

Gender differences, in particular, have been shown to be an important factor affecting cardiovascular KAP.[7] Few studies compared KAP between the male and female gender. One such study from Kuwait showed that knowledge about cardiovascular diseases was significantly higher among females compared to males.[6] Beyond gender, cardiovascular KAPs of a population may be affected by different cultures and locales. Previous studies have shown varying results reported from different countries.[8-10] Singapore is a multiethnic developed Asian city-state comprising 5.47 million people (74% Chinese, 13% Malay, and 9% Indian).[11] A previous study had examined knowledge of symptoms of heart attack and stroke in this country[12] but further studies are lacking.

In our Asian cohort, we aimed to analyse the KAP of patients towards CD and the pertinent factors that influence

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2]Department of Cardiology, National Heart Centre Singapore, Singapore
[3]Duke-NUS Medical School, Singapore
[*]These authors contributed equally to the study.
Address for Correspondence: Dr Shen Tong, 515 Dunman Road, #06-04, Singapore 439204.
Email: shentong827@gmail.com

such behaviour, in particular focusing on gender differences. This may potentially identify areas for development of more effective public health strategies.

Materials and Methods

We performed a cross-sectional survey on consecutive subjects attending the outpatient cardiac clinics at our institution for a period of 2 months from June to July 2014. Informed consent was obtained. A self-administered pen-and-paper questionnaire was distributed to the participants and completed questionnaires were collected at a central collection point in the clinics. An on-site investigator was available to answer any queries. Subjects who were unable to understand the questionnaire or declined to give consent were excluded. Ethics approval for the study was obtained from the Institutional Review Board.

Questionnaire

We developed the questionnaire to assess the KAPs of patients towards CD. The questionnaire was based on questionnaires on similar topics used in previous studies[7,13] and models of health behaviour.[14,15] The questionnaire was pilot-tested among patients with similar profiles to our target population and further refined to ensure that all the questions were easily understood and interpreted uniformly. The questionnaire gathered information regarding basic demographics such as age, sex, ethnicity, education level and housing type. The patient's KAP towards CD were also assessed. Questions on knowledge tested the patient's general knowledge towards healthy lifestyle choices, CD and its treatment. Questions on attitudes assessed patient's perception towards the above and questions on practices evaluated the actual compliance of the patients to these factors. Questions to ascertain the impact of financial concerns as well as knowledge of financial assistance schemes (Medisave, Medishield, Medifund, Community Health Assist Scheme [CHAS], and Chronic Disease Management Programme [CDMP]) were also included. Medisave is a government-mandated compulsory individual healthcare savings scheme; Medishield is a national healthcare insurance programme; Medifund is an endowment fund to help the needy with medical expenses; CHAS and CDMP are primary healthcare programmes to help subsidise the management of chronic diseases.

Patients were requested to rate their agreement with the statements in the questionnaire on a 4-point Likert scale or choose relevant option(s) from a list. The questionnaire was available in both English and Chinese.

Clinical information from the questionnaire was supplemented from the patients' hospital medical records including clinical characteristics and risk factors, physical examination findings and laboratory test results.

Statistical Analysis

To determine the sample size, we assumed that responses within each group were normally distributed with a standard deviation of 7%. To detect a true difference in means between groups of 2%, we required 259 participants per group to achieve power of 0.9 and $P = 0.05$.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 22.0 for Windows (SPSS Inc, Chicago, IL). The demographic and risk factor profile of the study population was characterised using descriptive statistics. To determine the KAP scores for each individual, responses were scored 1 point for a desired response and 0 for an undesired response. For instance, in response to a question which participants should agree to, "strongly agree" and "agree" were scored 1 while "strongly disagree" and "disagree" were scored 0. A total of 20 knowledge questions, 13 attitude questions and 12 practice questions were included. The scores for each section was then divided by the number of items in its respective section to obtain the final scores as percentages ± standard deviation (SD). Comparison between the 2 groups (male vs female) was performed using student's t-test for parametric data, Mann-Whitney U test for non-parametric data and chi-squared test for categorical data. The relationship between KAP scores was explored using bivariate correlational analyses and multivariate linear regression models.

Results

We approached 1406 patients, of which a total of 1000 (71.1%) (713 males, mean age 57 ± 12 years, 74% Chinese, 5% Malay and 13% Indian) patients consented to participate. These 1000 patients formed the study cohort. The incidence of diabetes, hypertension, hyperlipidaemia and prior coronary artery disease were significantly higher in males. Males were less likely to be either unemployed or homemakers. Males had significant higher body mass index (BMI) and diastolic blood pressure (Table 1).

KAP Scores

Overall Population

The overall KAP scores of our study population towards CD was 86.5 ± 8.1%, 91.9 ± 9.1% and 57.5 ± 18.7% respectively (Table 2). There was a significant correlation between knowledge scores and attitude scores ($r = 0.224$, $P < 0.001$) and knowledge scores and practice scores ($r = 0.114$, $P < 0.001$). There was no significant correlation between attitude and practice scores. Significant multivariate predictors of higher knowledge scores included female sex,

Table 1. Demographics of the Study Population

Demographics	Overall (n = 1000)	Males (n = 713)	Females (n = 287)	*P* Value*
Age	57.0 (12.7)	57.0 (12.7)	57.0 (12.6)	0.998
Ethnicity				0.085
Chinese	740 (74.0%)	517 (72.5%)	223 (77.7%)	
Malay	59 (5.9%)	42 (5.9%)	17 (5.9%)	
Indian	130 (13.0%)	105 (14.7%)	25 (8.7%)	
Others	71 (7.1%)	49 (6.9%)	22 (7.7%)	
Education				0.260
≤Secondary school/ITE	366 (37.3%)	254 (36.2%)	112 (40.0%)	
Polytechnic diploma/GCE A level	287 (29.2%)	202 (28.8%)	85 (30.4%)	
Degree/postgraduate	329 (33.5%)	246 (35.0%)	83 (29.6%)	
Occupation				<0.001
White collar§	388 (50.1%)	268 (49.1%)	120 (52.6%)	
Blue collar‖	131 (16.9%)	118 (21.6%)	13 (5.7%)	
Unemployed/homemaker	255 (32.9%)	160 (29.3%)	95 (41.7%)	
Housing				0.019
≤3-room public apartment¶	105 (11.4%)	66 (10.2%)	39 (14.4%)	
4- to 5-room public apartment¶	455 (49.6%)	339 (52.4%)	116 (42.8%)	
Private property	358 (39.0%)	242 (37.5%)	116 (42.8%)	
Marital status				0.013
Married	828 (85.5%)	608 (87.7%)	220 (80.0%)	
Divorced	31 (3.2%)	18 (2.6%)	13 (4.7%)	
Single	109 (11.3%)	67 (9.7%)	42 (15.2%)	
Smoking				<0.001
No	673 (72.0%)	425 (63.6%)	248 (93.9%)	
Ever smoker	262 (28.0%)	246 (36.7%)	16 (6.1%)	
Alcohol				<0.001
No	438 (46.9%)	259 (38.8%)	179 (67.0%)	
Ever drinker	496 (53.1%)	408 (61.2%)	88 (33.0%)	
Clinical characteristics				
Body mass index	25.6 (5.1)	26.2 (4.9)	24.3 (5.3)	<0.001
Systolic blood pressure	131.1 (17.6)	131.8 (17.2)	130 (18.4)	0.145
Diastolic blood pressure	70.7 (10.0)	72.2 (9.8)	67.1 (9.4)	<0.001
Diabetes mellitus	217 (21.7%)	173 (34.3%)	44 (15.3%)	0.002
Hypertension	480 (48.0%)	357 (50.1%)	123 (42.9%)	0.039
Hyperlipidaemia	614 (61.4%)	471 (66.1%)	143 (49.8%)	<0.001
Prior coronary artery disease	415 (41.5%)	353 (49.5%)	62 (21.6%)	<0.001
Prior congestive cardiac failure	38 (3.8%)	32 (4.5%)	6 (2.1%)	0.098
Atrial fibrillation	81 (8.1%)	62 (8.8%)	18 (6.3%)	0.246
Prior cerebrovascular accident	54 (5.4%)	40 (5.6%)	14 (4.9%)	0.758
HbA1C (%)†	6.3 (1.3)	6.4 (1.4)	6.0 (1.0)	0.007
LDL cholesterol (mmol/L)‡	2.7 (1.0)	2.6 (1.0)	3.0 (1.0)	<0.001

GCE: General Certificate of Education; HbA1C: Glycated haemoglobin; ITE: Institute of Technical Education

*Comparing males and females.

†623 patients with missing data (421 males, 202 females).

‡403 patients with missing data (267 males, 136 females).

§Refers to workers who perform job duties in an office setting.

‖Refers to workers who perform labour jobs or work with their hands.

¶Refers to heavily subsidised housing built by the government. Families with gross monthly income in excess of $10,000 are not eligible to directly purchase these subsidised apartments from the Housing and Development Board.

Mean and SD are reported for continuous data and frequency and percentages for categorical data.

Table 2. Scores and Zero-Order Correlation between Scores for Knowledge, Attitudes and Practices towards Cardiovascular Disease

	Overall (n = 1000)	Males (n = 713)	Females (n = 287)	*P* Value*
Knowledge score (%)	86.5 (8.1)	85.8 (8.0)	88.0 (8.2)	<0.001
Attitude score (%)	91.9 (9.1)	91.4 (9.4)	93.2 (8.3)	0.005
Practice score (%)	57.5 (18.7)	58.4 (18.4)	55.1 (19.3)	0.013

Correlation between scores	r	*P* Value	r	*P* Value	r	*P* Value
Knowledge score with attitude score	0.224	<0.001	0.218	<0.001	0.209	<0.001
Attitude score with practice score	0.030	0.359	0.049	0.196	0.004	0.952
Knowledge score with practice score	0.114	<0.001	0.158	<0.001	0.048	0.422

*Between males and females.
KAP scores range from 0% to 100%.

higher level of education, higher attitude and practice scores and prior coronary artery disease. Significant multivariate predictors of higher attitude scores included higher level of education and higher knowledge scores. Indian ethnicity was a significant predictor of lower attitude scores. Significant multivariate predictors of higher practice scores included male sex, higher level of education, older age, higher knowledge score and hypertension (Table 3).

Sex Stratified

Males had significantly lower knowledge scores (85.8 ± 8.0% vs 88.0 ± 8.2%, P <0.001), lower attitude scores (91.4 ± 9.4% vs 93.2 ± 8.3%, P = 0.005) and higher practice scores (58.4 ± 18.7% vs 55.1 ± 19.3%, P = 0.013) than females. In males, there was a significant correlation between knowledge and attitude score (r = 0.218, P <0.001) and knowledge and practice score (r = 0.158, P <0.001). In females, there was a significant correlation between knowledge and attitude score (r = 0.209, P <0.001). There was no significant correlation between attitude and practice scores in both sexes.

Significant multivariate predictors of higher knowledge scores in males included younger age, higher level of education, higher attitude and practice scores, and prior coronary artery disease; while that of females included higher level of education and employment, and higher attitude scores. Significant multivariate predictors of higher attitude scores in males included higher level of education and higher knowledge scores; while that of females included higher knowledge scores. Indian ethnicity and less affluent housing predicted lower attitude scores in females. Significant multivariate predictors of higher practice scores in males included older age, higher knowledge scores, and prior coronary artery disease; while that of females included older age and hypertension. Higher level of employment predicted lower practice scores in females (Table 4).

Specific Behaviours

Regarding compliance to the recommended daily intake of fruit and vegetables, overall 68.0% reported being compliant (66.6% males vs 71.6% females, P = 0.125). A total of 36.5% (38.2% males vs 32.2% females, P = 0.104) of the participants reported exercising ≥3 times per week while 28.7% (26.1% males vs 35.2% females, P = 0.005) exercised <1 time per week. Walking (76.1%), jogging (20.3%) and swimming (10.6%) were the most common modalities. Self-reported compliance to medications was 92.6% (93.6% males vs 80.0% females, P = 0.065). Of those non-compliant to medications, forgetting to take (50.7%), being too busy with work (25.9%) and having too many medications to take (8.8%) were the top 3 reasons. Compliance to follow-up was 85.3% (86.4% males vs 82.7% females, P = 0.169). Of those non-compliant to follow-up, being too busy (45.3%), follow-up visits being too expensive (34.9%) and visits being too troublesome to attend (16.0%) were the top 3 reported reasons.

A total of 33.4% and 19.1% of patients believed that monitoring for hypertension and diabetes mellitus respectively should only be done during clinic visits. Patients chose chest pain (94.4%), shortness of breath (85.9%) and sweating (78.1%) as the 3 most common symptoms of heart attack. A majority of patients were able to distinguish between symptoms suggestive of upper respiratory tract infection and cardiac symptoms. In response to symptoms of a heart attack, 60.3% chose to call the ambulance, 10.8% chose to wait to see if the symptoms get better, 10% would visit the general practitioner, 9.4% would go to the hospital themselves, and 2% would seek advice from family members.

When asked about the affordability of healthcare, 73.3% were worried about the cost of treatment. High cost of medications (43.8%), high cost of consultation (42.0%) and the lack of government support (13.9%) were cited as

Table 3. Multivariate Linear Regression of Scores for Knowledge, Attitudes and Practice towards Cardiovascular Disease for Overall Cohort

	Knowledge Score			Attitude Score			Practice Score		
	β	95% CI for β	*P* Value	β	95% CI for β	*P* Value	β	95% CI for β	*P* Value
Sex									
Male	-2.797	-3.994 to -1.600	<0.001	-1.418	-2.861 to 0.025	0.054	3.173	0.426 to 5.920	0.024
Ethnicity									
Others	0.648	-1.365 to 2.662	0.528	-1.166	-3.548 to 1.217	0.337	3.803	-0.733 to 8.340	0.100
Indian	0.056	-1.531 to 1.644	0.945	-2.394	-4.293 to -0.496	0.014	3.170	-0.432 to 6.772	0.084
Malay	-0.218	-2.474 to 2.038	0.850	0.178	-2.508 to 2.863	0.897	-2.720	-7.846 to 2.407	0.298
Chinese*	NA								
Age	-0.046	-0.099 to 0.006	0.086	-0.010	-0.073 to 0.053	0.763	0.488	0.373 to 0.303	<0.001
Education									
Polytechnic diploma/GCE A level	1.708	0.414 to 3.003	0.010	0.899	-0.647 to 2.445	0.254	1.914	-1.029 to 4.857	0.202
Degree/postgraduate	3.584	2.241 to 4.926	<0.001	2.665	1.044 to 4.286	0.001	3.222	0.129 to 6.314	0.041
≤Secondary school/ITE*	NA								
Occupation									
Blue collar	0.369	-1.275 to 2.014	0.659	-1.221	-3.190 to 0.748	0.224	-1.457	-5.195 to 2.280	0.444
White collar	0.741	-0.418 to 1.901	0.210	-0.704	-2.091 to 0.684	0.320	-1.590	-4.223 to 1.043	0.236
Unemployed/homemaker*	NA								
Housing									
≤3-room public apartment	-1.177	-3.022 to 0.668	0.211	0.337	-1.856 to 2.529	0.910	1.414	-2.759 to 5.586	0.506
4- to 5-room public apartment	-0.185	-1.305 to 0.935	0.746	0.512	-0.828 to 1.851	0.453	-1.771	-4.312 to 0.770	0.172
Private property*	NA								
Marital status									
Married	0.232	-1.454 to 1.918	0.787	0.575	-1.448 to 2.598	0.577	-0.549	-4.383 to 3.284	0.779
Divorced	-2.221	-5.541 to 1.099	0.190	2.821	-1.100 to 6.742	0.158	-3.190	-10.746 to 4.367	0.408
Single*	NA								
Knowledge score	NA			0.215	0.135 to 0.294	<0.001	0.266	0.113 to 0.419	0.001
Attitude score	0.148	0.092 to 0.204	<0.001	NA			0.028	-0.101 to 0.157	0.667
Practice score	0.051	0.022 to 0.081	0.001	0.009	-0.026 to 0.044	0.619			
Body mass index	-0.005	-0.109 to 0.099	0.930	0.091	-0.033 to 0.215	0.152	-0.096	-0.332 to 0.140	0.425
Diabetes mellitus	0.257	-1.110 to 1.624	0.712	0.851	-0.777 to 2.479	0.305	2.091	-0.998 to 5.181	0.184
Hypertension	0.301	-0.831 to 1.433	0.602	-0.203	-1.560 to 1.153	0.768	2.895	0.330 to 5.459	0.027
Hyperlipidaemia	-0.237	-1.456 to 0.982	0.702	0.264	-1.195 to 1.723	0.723	0.316	-2.457 to 3.008	0.823
Prior coronary artery disease	1.321	0.135 to 2.507	0.029	-0.820	-2.239 to 0.598	0.257	2.454	-0.241 to 5.149	0.074

CI: Confidence interval; GCE: General Certificate of Education; ITE: Institute of Technical Education; NA: Not applicable
*Reference group.

Table 4. Sex Stratified Significant Multivariate Predictors of Knowledge, Attitude and Practice Scores

	Knowledge Score				**Attitude Score**				**Practice Score**		
Predictor	β	95% CI	*P* Value	Predictor	β	95% CI	*P* Value	Predictor	β	95% CI	*P* Value
Males											
Age	-0.062	-0.120 to -0.004	0.036	Degree/postgraduate	2.743	0.784 to 4.703	0.006	Age	0.452	0.326 to 0.579	<0.001
Polytechnic diploma/ GCE A level	1.849	0.334 to 3.364	0.017	Knowledge score	0.227	0.129 to 0.325	<0.001	Knowledge score	0.338	0.161 to 0.516	<0.001
Degree/ postgraduate	3.539	1.989 to 5.088	<0.001					Prior coronary artery disease	3.335	0.326 to 6.344	0.030
Attitude score	0.145	0.082 to 0.207	<0.001								
Practice score	0.067	0.032 to 0.102	<0.001								
Prior coronary artery disease	1.354	0.018 to 2.689	0.047								
Females											
Degree/ postgraduate	4.959	2.359 to 7.558	<0.001	Indian	-4.437	-8.001 to -0.874	0.015	Age	0.490	0.269 to 0.712	<0.001
White collar	2.142	0.055 to 4.229	0.044	≤3 room public apartment	-3.324	-6.630 to -0.018	0.049	White collar	-4.890	-9.750 to -0.030	0.049
Attitude score	0.137	0.015 to 0.259	0.028	Knowledge score	0.144	0.015 to 0.273	0.028	Hypertension	6.643	1.471 to 11.816	0.012

CI: Confidence interval; GCE: General Certificate of Education

the 3 most common reasons. Awareness of support schemes was as follows: medical social worker (67.2%), Medisave (81.9%), Medishield (79.5%), Medifund (80.5%), CHAS (62.3%) and CDMP (41.2%).

Discussion

In our cohort, there was high knowledge and attitude scores and relatively lower practice scores. There were also significant correlations between knowledge and attitude/practice scores with noted gender differences.

The high knowledge and attitudes scores in our cohort could be attributed to Singapore being a developed city state with high literacy rates.[16] Most patients were able to identify behavioural cardiovascular risk factors such as smoking, unhealthy diet and lack of exercise. Prior studies in developing countries with poor education levels[17-19] have shown lower levels of knowledge as compared to those developed countries.[10,20] In Nepal, there was limited knowledge of cardiovascular health with 60% being unable to identify any heart attack symptoms.[7] In contrast, the majority of Vietnamese Americans were able to spontaneously mention chest pain as a symptom of heart attack and 85% knew that they should immediately activate the emergency services should they suspect a heart attack.[9]

We found a significant correlation between knowledge and attitudes/practice scores in our study. Knowledge forms the basis of a good foundation to better attitudes and practices and this has been shown in models of behavioural change. The Health Belief Model states that the likelihood of taking action to prevent illnesses depends on factors such as perceived susceptibility, disease severity, and the benefits and barriers of behaviour change.[14] As a result, having better knowledge would then alter the balance of the model constructs, leading to better attitudes and practices. Studies have shown that improving patients' health literacy can empower them to improve their health outcomes.[21] In Malaysian women, there was significant correlation between KAP scores which were independent of other sociodemographic factors.[22]

However, the correlation did not translate proportionally to good practice scores in our study. As discussed above, knowledge does impact practices; however, this relationship may also be influenced by many other factors. A study among patients with cardiovascular diseases and risk factors found that those at moderate risk had better perceptions towards exercise and weight loss as compared to those with established cardiovascular disease but this did not translate into actual practice.[3] Another study on influenza also demonstrated poor practice scores despite high knowledge scores and good correlation between knowledge and practice scores.[13] A potential explanation exists in health behaviour theories such as the social cognitive theory and the theory of reasoned action.[15] There are many factors influencing a person's health behaviour, and knowledge and attitude are only 2 components in the pathway. For example, in the social cognitive theory, constructs and other personal and environmental determinants also play crucial roles. Valente et al also suggested that each behaviour change model utilises different order of KAP with each individuals fitting into each model differently;[23] specific interventions may be required to be tailored to the individual. Thus, although it would be worthwhile to focus on public health interventions to improve the knowledge of the population, the limitations of such measures should be recognised.

Socioeconomic Influences

Socioeconomic status (SES) plays an important part in the long-term outcome of patients with CD.[24] People of lower SES are known to be at higher risk of CD, especially in high-income countries.[25] Traditionally, education level, employment level and housing type have been used a proxy for SES as in our study.[26] In the overall cohort, higher education levels resulted in higher knowledge and attitude scores. In females, higher level of employment resulted in higher knowledge scores while less affluent level of housing resulted in lower attitude scores. This is consistent with other studies that also showed links between lower SES and poorer KAP scores.[8,10,22,27] In Iran, participants with higher education levels had significantly better knowledge towards CD when compared to those with lower education levels.[27] In a study of Canadian residents, higher income was associated with better knowledge of cardiovascular risk factors such as smoking, elevated cholesterol and lack of exercise.[10] Emphasis needs to be placed on reaching out to this section of the population. Unexpectedly, higher level of employment in females in our study resulted in lower practice scores and could possibly be explained by lack of time to focus on health needs.

Gender Influences

Current literature lacks data on gender differences on cardiovascular KAPs. In our cohort, females had significantly higher knowledge and attitude scores but lower practice scores as compared to males. A significantly greater proportion of females did little/no exercise and there was a trend towards lower compliance to medications and follow-up.

The higher knowledge and attitude scores found in our study is consistent with results from prior studies.[27] An Iranian study showed higher mean knowledge scores in women compared to men.[27] One possible explanation for the higher knowledge and attitude scores is that women

are more proactive in seeking health information. A study conducted in Finland looking into the gender differences in health information-seeking behaviour concluded that women were more interested in and reported more active seeking of health-related information.[28] Furthermore, women also received more health-related information from family members as compared to men. This exposure to health information has been shown to result in better knowledge.[29] Hence, in order to improve gender equity in health, men need to be engaged and empowered to utilise the information widely available from various sources. Public health interventions could also be modified to be more gender specific. This conclusion is largely congruent with the result of an analysis of 5 internationally recognised health promotion frameworks which emphasised that gender has never been properly integrated as a factor critical to successful health promotion.[30] Another explanation for higher knowledge and attitude scores among women is that in our local setting, a woman's traditional responsibility to the family involves taking care of the non-financial household matters, and this may extend to include acquiring health-related knowledge and acting as a primary custodian of the family's health.[31,32] The lower practice scores in Asian women could potentially be a result of her prioritising her role as primary caregiver over her health needs, thus, acting as a barrier towards behavioural change.

The higher practice scores in males is also congruent with other studies. In a study of patients postmyocardial infarction, it was found that women were less likely than men to participate in cardiac rehabilitation.[33] The higher practice scores in males could be explained by the fact that males had higher burden of both modifiable and non-modifiable cardiovascular risk factors. In a study of the general population of Seychelles, individuals who were aware that they had hypertension made greater efforts to reduce salt intake and visit a doctor.[4] In another study comparing the health-related behaviour among those with cardiovascular diseases and risk factors, participants with established cardiovascular disease reported higher levels of exercise and better maintenance of desired weight.[3] This finding could be explained by the Health Belief Model whereby individuals who are aware of their cardiovascular risk factors have higher perceived threat, leading to increased likelihood of engaging in cardiovascular health-promoting behaviour.[14] In our study, a prior history of coronary artery disease was a significant predictor of knowledge and practice scores in males, further supporting this explanation.

This study has important public health implications. Public health campaigns targeting the various subsets of at-risk patients to improve their knowledge are important tools. These campaigns need to be pitched at the correct level. Of note, a substantial group of patients were not aware of support schemes like the CHAS and CDMP despite governmental publicity via television commercials, advertisements and posters. This highlights the important role healthcare staff have to play in making aware to the patient the availability of such schemes. For the general public, beyond the routine publicity, novel ways to reach out should be considered (eg. publicity at common areas like food centres, supermarkets). Efforts to bridge the gap between knowledge and actual practice is another area of work. Individual-level patient education by dedicated personnel (eg. nurse educators) is one possible solution.

Limitations

Males were unintentionally represented in higher proportions (71.3%) in our study, reflecting the higher CD burden in males.[1] There exists the potential of bias from the phenomenon of social desirability, whereby individuals become unwilling to admit socially unacceptable KAP in order to leave a more positive impression.[34,35] This is inherent in most similar studies. The impact of KAPs on CD outcomes were not assessed in this cross-sectional survey and will be the subject of future studies. This study was also limited by the availability of only English and Chinese versions of the questionnaire. Therefore, there was likely a selection bias in terms of ethnicity and SES, which may affect the applicability of the results to these subgroups. For example, although Malays comprised 15% of the overall population in the 2014 census, they made up only 5.9% of our study population. Future studies will include Malay and Tamil versions of the questionnaires. Similarly, our study reported higher proportions staying in private housing and lower proportions in 1-, 2- and 3-room public flats.[36] This could suggest that the study population was likely represented by more educated patients who could read the self-administered questionnaire. Another limitation is that this study was conducted in the outpatient setting of a tertiary centre for cardiovascular care, limiting its generalisability to the normal healthy population. However, it does highlight potential gaps in the public's KAP as it can be reasonably inferred that the general public would likely have equal, if not lower, levels of these attributes. Further studies in other population groups (eg. polyclinics, inpatients, etc.) would help validate the findings of our study.

Conclusion

In our Asian cohort, knowledge of cardiovascular health plays a significant role in influencing attitudes and practices. There exists significant gender differences in KAPs. Future public health campaigns may potentially focus on improving general knowledge as well as addressing these gender differences to promote healthy behaviour.

REFERENCES

1. Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104:2746-53.
2. Chen W, Yu Y, Glaser K. The knowledge and attitudes of coronary heart disease prevention among middle and older aged people in a community in Taipei. Taiwan Geriatr Gerontol 2009;4:251-62.
3. Robinson JG, Fox KM, Grandy S. Attitudes about health and health-related behaviors in patients with cardiovascular disease or at elevated risk for cardiovascular disease. Prev Cardiol 2009;12:136-43.
4. Aubert L, Bovet P, Gervasoni JP, Rwebogora A, Waeber B, Paccaud F. Knowledge, attitudes, and practices on hypertension in a country in epidemiological transition. Hypertension 1998;31:1136-45.
5. Lambert C, Vinson S, Shofer F, Brice J. The relationship between knowledge and risk for heart attack and stroke. J Stroke Cerebrovasc Dis 2013;22:996-1001.
6. Awad A, Al-Nafisi H. Public knowledge of cardiovascular disease and its risk factors in Kuwait: a cross-sectional survey. BMC Public Health 2014;14:1131.
7. Vaidya A, Aryal UR, Krettek A. Cardiovascular health knowledge, attitude and practice/behaviour in an urbanising community of Nepal: a population-based cross-sectional study from Jhaukhel-Duwakot Health Demographic Surveillance Site. BMJ Open 2013;3:e002976.
8. Dodani S, Mistry R, Khwaja A, Farooqi M, Qureshi R, Kazmi K. Prevalence and awareness of risk factors and behaviours of coronary heart disease in an urban population of Karachi, the largest city of Pakistan: a community survey. J Public Health (Oxf) 2004;26:245-9.
9. Nguyen TT, Liao Y, Gildengorin G, Tsoh J, Bui-Tong N, McPhee SJ. Cardiovascular risk factors and knowledge of symptoms among Vietnamese Americans. J Gen Intern Med 2009;24:238-43.
10. Potvin L, Richard L, Edwards AC. Knowledge of cardiovascular disease risk factors among the Canadian population: relationships with indicators of socioeconomic status. CMAJ 2000;162:S5-11.
11. Monthly Digest of Statistics Singapore, March 2015: Department of Statistics, Ministry of Trade & Industry, Republic of Singapore 2015. Available at: http://www.singstat.gov.sg/docs/default-source/default-document-library/publications/publications_and_papers/reference/monthly_digest/mdsmar15.pdf. Accessed on 14 April 2015.
12. Quah JLJ, Yap S, Cheah SO, Ng YY, Goh ES, Doctor N, et al. Knowledge of signs and symptoms of heart attack and stroke among Singapore residents. BioMed Research International 2014;2014:8.
13. Yap J, Lee VJ, Yau TY, Ng TP, Tor PC. Knowledge, attitudes and practices towards pandemic influenza among cases, close contacts, and healthcare workers in tropical Singapore: a cross-sectional survey. BMC Public Health 2010;10:442.
14. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the Health Belief Model. Health Educ Q 1988;15:175-83.
15. Redding C, Rossi S, Rossi R. Health behavior models. Int Electron J Health Educ 2009;3:180-93.
16. Gazmararian JA, Williams MV, Peel J, Baker DW. Health literacy and knowledge of chronic disease. Patient Educ Couns 2003;51:267-75.
17. Khan MS, Jafary FH, Faruqui AM, Rasool SI, Hatcher J, Chaturvedi N, et al. High prevalence of lack of knowledge of symptoms of acute myocardial infarction in Pakistan and its contribution to delayed presentation to the hospital. BMC Public Health 2007;7:284.
18. Minh An DT, Van Minh H, Huong le T, Giang KB, Xuan le TT, Hai PT, et al. Knowledge of the health consequences of tobacco smoking: a cross-sectional survey of Vietnamese adults. Glob Health Action 2013;6:1-9.
19. Saeed O, Gupta V, Dhawan N, Streja L, Shin JS, Ku M, et al. Knowledge of modifiable risk factors of coronary atherosclerotic heart disease (CASHD) among a sample in India. BMC Int Health Hum Rights 2009;9:2.
20. Schweigman K, Eichner J, Welty TK, Zhang Y. Cardiovascular disease risk factor awareness in American Indian communities: the strong heart study. Ethn Dis 2006;16:647-52.
21. Angelmar R, Berman P. Patient empowerment and efficient health outcomes. Report 3 from Sustainable Healthcare Financing: new approaches for new outcomes conference, Helsinki February 2007. Available at: http://med.over.net/javne_datoteke/novice/datoteke/10483-Report_3.pdf. Accessed on 14 April 2015.
22. Yahya R, Muhamad R, Yusoff H. Association between knowledge, attitude and practice on cardiovascular disease among women in Kelantan, Malaysia. Int J Collaborative Res Intern Med Public Health 2012;4:1507-23.
23. Valente TW, Paredes P, Poppe PR. Matching the message to the process: the relative ordering of knowledge, attitudes, and practices in behavior change research. Hum Commun Res 1998;24:366-85.
24. Rathore SS, Masoudi FA, Wang Y, Curtis JP, Foody JM, Havranek EP, et al. Socioeconomic status, treatment, and outcomes among elderly patients hospitalized with heart failure: findings from the National Heart Failure Project. Am Heart J 2006;152:371-8.
25. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. Nat Rev Cardiol 2009;6:712-22.
26. Latest Data: Singapore Department of Statistics; 2014. Available at: http://www.singstat.gov.sg/statistics/latest-data#19. Accessed on 14 April 2015.
27. Attarchi M, Mohammadi S, Nojomi M, Labbafinejad Y. Knowledge and practice assessment of workers in a pharmaceutical company about prevention of coronary artery disease. Acta Med Iran 2012;50:697-703.
28. Ek S. Gender differences in health information behaviour: a Finnish population-based survey. Health Promot Int 2015;30:736-45.
29. Tedesco LMR, Di Giuseppe G, Napolitano F, Angelillo IF. Cardiovascular diseases and women: knowledge, attitudes, and behavior in the general population in Italy. BioMed Research International 2015;2015:7.
30. Gelb K, Pederson A, Greaves L. How have health promotion frameworks considered gender? Health Promot Int 2012;27:445-52.
31. Umberson D. Gender, marital status and the social control of health behavior. Soc Sci Med 1992;34:907-17.
32. Norcross WA, Ramirez C, Palinkas LA. The influence of women on the health care-seeking behavior of men. J Fam Pract 1996;43:475-80.
33. Witt BJ, Jacobsen SJ, Weston SA, Killian JM, Meverden RA, Allison TG, et al. Cardiac rehabilitation after myocardial infarction in the community. J Am Coll Cardiol 2004;44:988-96.
34. Welte JW, Russell M. Influence of socially desirable responding in a study of stress and substance abuse. Alcohol Clin Exp Res 1993;17:758-61.
35. Nothwehr F, Elmer P, Hannan P. Prevalence of health behaviors related to hypertension in three blood pressure treatment groups: the Minnesota Heart Health Program. Prev Med 1994;23:362-8.
36. HDB Annual Report 2013/2014 2014 [21 May 2015]. Available at: http://www10.hdb.gov.sg/eBook/ar2014/keystatistics/index.html. Accessed on 14 April 2015.

Commentary

Personal Recovery in Serious Mental Illness: Making Sense of the Concept

Madeline WZ Lim, [1]*B Psych*, Gary Remington, [2,3]*MD, PhD, FRCPC*, Jimmy Lee, [1,4,5]*MBBS, M Med (Psychiatry), FAMS*

Abstract

Traditionally, clinicians and healthcare users alike use the term "recovery" to imply a return to a premorbid state. This form of clinical recovery is objective, measureable and is a clear health outcome. In the past decade, an alternative to clinical recovery, also known as personal recovery, has gained traction in mental health and has impacted numerous mental health systems. Originally, personal recovery was conceptualised as an individually unique ongoing process for individuals with serious mental illness that emphasises on growth and potential for recovery, but it has also been proposed to be a clinical outcome for mental health professionals. In this commentary, we discuss the differences in the 2 models of recovery and attempt to illustrate the concepts behind personal recovery so as to clarify its usage in people with serious mental illnesses.

Ann Acad Med Singapore 2017;46:29-31

Key words: Post-traumatic growth, Resilience, Stigma

The literature surrounding the recovery movement in mental health is abound and in this movement, we have heard a growing optimism in the possibility of recovery from serious mental illness.

The term "recovery" has connotations of regaining a premorbid form of health. Originally used in acute medical conditions,[1] it refers to the remission of symptoms and regaining of functional independence, as well as abilities to lead a "normal" life. Particularly, it refers to the return to the normal state of health before the "tragedy" struck. For some time, mental health professionals pursued the same goals—a return to a premorbid state or what is now termed "clinical recovery".[2] Clinical recovery seemed achievable with strict compliance to well laid out treatment plans and has the advantages of objectivity, invariance and can be easily measured as an outcome.[2] However, we now acknowledge that the traditional understanding of recovery is no longer appropriate in chronic medical conditions, as a return to a premorbid form of health is not expected. Similarly, the chronic nature of serious mental illness might have been forgotten; as such, misguided use of recovery has influenced mental health.[1]

The other form of recovery, as reported by mental health consumers, tells of an idiosyncratic and subjective story of recovery, termed as "personal recovery".[3] Commonly cited descriptions describe it as: "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills, and/or roles. It is a way of living a satisfying, hopeful, and contributing life even within the limitations caused by illness. Recovery involves the development of new meaning and purpose in one's life as one grows beyond the catastrophic effects of mental illness."[4] Therefore, personal recovery entails an ongoing learning process and recalibration of one's life, closely connected to the terms "post-traumatic growth" and "resilience". Just as a person with paraplegia can continue to pursue his or her aspirations and goals in spite of the physical impairments,[1] similarly, a person with serious mental illness can still pursue his or

[1]Research Division, Institute of Mental Health, Singapore
[2]Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Canada
[3]Department of Psychiatry, University of Toronto, Canada
[4]Department of General Psychiatry 1, Institute of Mental Health, Singapore
[5]Office of Clinical Sciences, Duke-NUS Medical School, Singapore
Address for Correspondence: Dr Jimmy Lee, Department of General Psychiatry 1, Institute of Mental Health, 10 Buangkok View, Singapore 539747.
Email: jimmy_lee@imh.com.sg

her aspirations despite the mental impairments.

Resilience is the ability to tolerate and/or dissipate, stay unaffected or undisrupted despite experiencing strong forces that might cause others to break. One's innate self-healing and self-righting tendencies helps one to carry on with life as per usual without experiencing the predicted negative health and mental health effects.[5] Personal recovery, on the other hand, is another form of resilience when one initially breaks down (causing disruption in functioning) as a result of stressors, but later learns to overcome or accommodate the broken places and strengthen themselves so as to never break again.[5] Therefore, the recovering person while is not invulnerable to stressors, remains capable of deploying reserve capacities to help oneself to cope effectively with life.[5]

This process where a person becomes resilient is enabled by post-traumatic growth, which refers to the "positive psychological change experienced as a result of the struggle with highly challenging life circumstances".[6] The experience of serious mental illness has a profound impact on an individual's life above and beyond the symptoms. These include interruptions of normal life events, social stigma, the loss of self-esteem and avoidance from friends and even family.[7] This is a traumatic-like experience that requires the individual to address during recovery. Although the "trauma" of mental illness has changed the individual's personal identity and understanding of the world forever, the individual is able to reconcile and embrace what has happened to him or her, and incorporate it into one's life in a way that the impact of the trauma is largely in control or is no longer intrusive or disruptive.[1] This is possible as the recovering individual whom still possesses self-righting capacities and inherent growth potential,[5] recognises that one is still a whole person despite the psychiatric disability and thus, the newly expanded self can manage by minimising the illness into one aspect of a multidimensional self and through pulling all available resources together. In all, one rises to a higher level of functioning that involves growth and expansion of one's capacities,[3] develops the ability to bounce back, possesses a stronger capacity to respond to adversities in the future, and springs forward to something greater than whom one has been before despite the impaired aspects.

Overall, to say that recovery in mental health is the return to a premorbid state of health is invalid. This is especially in the case of serious mental illness as the premorbid state of health can include lack of support, emotional traumas, and poor relationships with significant others while growing up, losses, and emotional wounds.[8] These psychosocial experiences are largely indelible and might even exert long-term neurobiological sequelae.[9] Moreover, to take recovery as a return to a premorbid form of health would negate all gains made in the process of recovery. Therefore, recovery in this sense should be in accordance with the quote: "don't look back, go forward" instead of returning to the exact causes of the existing mental health difficulties, since what lies ahead is more important. To this end, efforts by various local community agencies to reintegrate people with mental illnesses back into society and to combat the barriers of personal recovery are indeed commendable.

Both forms of recovery—clinical and personal—are relevant in physical and mental conditions. While clinical recovery is important, personal recovery should be given equal attention in order to provide holistic care as it considers the individual's subjective appraisal of his or her functioning and satisfaction with life.[10] Personal recovery is a higher hurdle and longer term goal that should be addressed. Particularly in serious mental illnesses, patients have to face added pressures of social stigma, discrimination and a loss of identity, where the sense of self is dictated by the mental illness. Having a weak sense of self jeopardises itself even more when faced with these stigmas[11] since the experience of oneself as barren results in the inability to use alternative internal experiences to reject these stigmas. Recovering a sense of self is one of the core processes or domains of recovery as seen in first-episode schizophrenia patients[12] and in patients with prolonged psychiatric disorders.[13] In this process, it starts with the discovery that a part of the self is still present and undefined by the illness. Then, one can tap on this part of the self to rebuild one's life despite the illness. This discovery is the first ignition of hope, which lies a possibility of being functional despite the illness. With hope, one can look ahead and experience the inward-looking recovery journey in becoming a resilient person who can face all future life circumstances, without breaking.

Acknowledgement

Dr Jimmy Lee is supported by the National Healthcare Group's Clinician Scientist Career Scheme.

REFERENCES

1. Davidson L, O'Connell MJ, Tondora J, Lawless M, Evans AC. Recovery in serious mental illness: a new wine or just a new bottle? Professional Psychology: Research and Practice 2005;36:480-7.
2. Slade M, Amering M, Oades L. Recovery: an international perspective. Epidemiol Psichiatr Soc 2008;17:128-37.
3. Leamy M, Bird V, Le Boutillier C, Williams J, Slade M. Conceptual framework for personal recovery in mental health: systematic review and narrative synthesis. Br J Psychiatry 2011;199:445-52.

4. Anthony WA. Recovery from mental illness: the guiding vision of the mental health service system in the 1990s. Psychiatr Rehabil J 1993;16:11-23.
5. Ridgway P. Resilience and recovery from psychiatric disabilities: links in concepts and research. A working paper. Lawrence, KS: University of Kansas;2004.
6. Tedeschi RG, Calhoun LG. Target Article: 'Posttraumatic Growth: Conceptual Foundations and Empirical Evidence'. Psychological Inquiry 2004;15:1-18.
7. Bellack A. Scientific and consumer models of recovery in schizophrenia: concordance, contrasts, and implications. Schizophr Bull 2006;32:432-42.
8. Bentall RP. Madness explained: psychosis and human nature. London, England: Penguin Books;2004.
9. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009;65:760-9.
10. Kukla M, Lysaker PH, Roe D. Strong subjective recovery as a protective factor against the effects of positive symptoms on quality of life outcomes in schizophrenia. Compr Psychiatry 2014;55:1363-8.
11. Hasson-Ohayon I, Mashiach-Eizenberg M, Elhasid N, Yanos PT, Lysaker PH, Roe D. Between self-clarity and recovery in schizophrenia: reducing the self-stigma and finding meaning. Compr Psychiatry 2014;55:675-80.
12. Romano DM, McCay E, Goering P, Boydell K, Zipursky R. Reshaping an enduring sense of self: the process of recovery from a first episode of schizophrenia. Early Interv Psychiatry 2010;4:243-50.
13. Davidson L, Strauss JS. Sense of self in recovery from severe mental illness. Br J Med Psychol 1992;65:131-45.

A 13-Year Single Institutional Experience with Definitive Radiotherapy in Hypopharyngeal Cancer

Dear Editor,

Patients with hypopharyngeal carcinoma often present with locally advanced disease. Treatment options are usually multimodality and involve surgery, radiotherapy (RT) and chemotherapy. Definitive RT with or without chemotherapy present a functional organ preservation strategy in selected patients or in patients with extensive inoperable local disease. Whereas upfront surgery followed by adjuvant RT may be more appropriate in patients with disease which limits the adequate recovery of speech and swallowing function with organ preservation strategy. Patients with significant cartilage destruction or bilateral vocal cord destruction may also have better function after laryngectomy and rehabilitation following surgery.

The landmark VA trial investigated the feasibility of organ preservation in laryngeal cancer patients using sequential chemotherapy-RT as an alternative to upfront surgery.[1] More than half of the patients had their larynx preserved with comparable survival to the surgical group. This encouraging result opened new avenues for application of this strategy in patients with locally advanced cancer of other head and neck primary sites. Similar conclusion was also established in the subsequent EORTC 24981 trial which included 152 hypopharyngeal cancer patients.[2,3]

Concomitant radio-chemotherapy (CRT) strategy arose from the RTOG 91-11 trial and meta-analysis which demonstrated improved loco-regional control (LRC) and laryngeal preservation rates compared to induction chemotherapy followed by radical RT.[4-7] This approach is now widely practised in many centres worldwide.

We adopted the concurrent CRT approach as the organ preservation strategy in treating selected patients with hypopharyngeal cancer. The aim of our study was to retrospectively review the outcome following curative intent RT with or without chemotherapy in hypopharyngeal cancer patients treated in our centre and also to determine the prognostic factors on LRC and survival in this group of patients.

Materials and Methods

This is a retrospective analysis of all patients with hypopharyngeal cancer treated with curative intent RT in our Department of Radiation Oncology in National Cancer Centre Singapore (NCCS) between January 2000 and December 2013. Pretreatment evaluation included history taking, clinical examination, endoscopic examination of the upper aero-digestive tract and computer tomography of the neck and chest. The patients were discussed in a multidisciplinary tumour board and treatment decisions were made based on stage of disease, performance status and the anticipated swallowing and speech outcome. There were a total of 58 eligible patients during this period.

Radiotherapy

All patients were immobilised with customised thermoplastic mask and treated with 6MV photon encompassing the primary bearing area and regional lymph nodes. Patients who received upfront radical RT were treated with 66-70 Gy delivered in 33-35 fractions, whereas patients who received adjuvant RT were treated with 60-66 Gy in 30-33 fractions.

The gross tumour volume (GTV) was defined as any visible gross disease based on radiological and clinical findings. High risk clinical target volume (CTV) is an expansion of 5-10 mm margin around the GTV, and with editing off natural tumour barriers. This volume was treated with 66-70 Gy. Intermediate risk CTV included the possible local subclinical infiltration of the primary site as well as first echelon nodal stations and was prescribed 60 Gy. Low risk CTV included regional nodal stations which are not first echelon nodes and were not adjacent to the levels of involved nodes and was prescribed 50 Gy. In the adjuvant setting, the tumour bed and involved nodal stations were treated to 60 Gy with a further 6 Gy boost to areas of extracapsular extension or close/positive margin.

Twenty-nine of 58 patients were treated using a 2-dimensional (2D) technique and the other 29 with intensity modulated radiotherapy (IMRT). In the IMRT technique, all dose levels were delivered within the same plan with the higher doses effected through a simultaneous integrated boost. In the 2D technique, the RT was delivered via 2 shaped lateral parallel opposed fields with a low anterior neck match in 2 or 3 phases using shrinking field technique.

Follow-Up

Patients were reviewed at least once a week during RT. Thereafter, patients were reviewed once a month for the first year, 2-monthly for the second year, 3-to-4

monthly for the third year and 6-monthly after the third year. Treatment response was assessed by clinical and endoscopic examination, aided by computed tomography (CT) or magnetic resonance imaging (MRI) at 3 months post-RT, and repeated when warranted.

Statistical Analysis

Kaplan-Meier curves were generated for all the survival analysis. The Cox proportional hazards regression was used to analyse the prognostic factors for overall survival (OS), progression-free survival (PFS) and LRC. A two-sided *P* value <0.05 was considered statistically significant. Duration of all types of survival analysis was computed from the date of diagnosis of hypopharyngeal cancer. Prognostic factors identified were age, gender, T stage (T1/2 vs T3/4), N stage (N0/1 vs N2/3), group stage (stage II/III vs IVA/B), RT technique (IMRT vs 2D), surgery (yes vs no), chemotherapy (yes vs no), smoking status (yes vs no), and tumour subsite (pyriform fossa vs others). Statistical analyses were performed using the STATA 12.0 software (Stata Corp, College Station, 2012, TX, USA).

Results

Patient Characteristics

Out of 58 hypopharyngeal cancer patients who had definitive RT treatment, 51 (87.9%) were male and the median age of all hypopharyngeal cancer patients in this study was 66.5 years; 70.7% of hypopharyngeal cancer patients in this study had stage IVA disease (Table 1).

Fifteen patients underwent surgery followed by adjuvant RT. Out of the 15 patients, 14 had neck dissection, 4 had total laryngectomy, 6 had laryngopharyngectomy, 2 had partial pharyngectomy and 3 had pharyngo-laryngo-esophagectomy. The remaining 43 patients received upfront radical RT.

Concurrent chemotherapy was administered to 33 patients and consisted of mainly cisplatin monotherapy. The median RT dose delivered was 70 Gy in 35 fractions, with a median overall treatment time of 47 days. Half of the patients were treated with IMRT, and the other half were treated with 2D RT. Other demographics and clinical characteristics together with their treatment characteristics are summarised in Table 1.

Response to Treatment

Fifty-one patients achieved complete response at 3 months post-RT whereas 7 patients had persistent/residual disease (3 in the primary site only, 3 in the primary and regional nodes and 1 in the regional nodes only). Out of these 7 patients, 2 patients were inoperable or unfit for salvage surgery and received palliative treatment. The remaining

Table 1. Demographics and Clinical Characteristics of Hypopharyngeal Cancer Patients in National Cancer Centre Singapore

Variable	No.	%
Total	58	100
Age at diagnosis		
Median (range)	66.5 (44 – 87)	
Age, years		
≤70	38	65.5
>70	20	34.5
Gender		
Male	51	87.9
Female	7	12.1
Subsite		
Posterior wall	18	31.0
Pyriform fossa	32	55.2
Postcricoid space	8	13.8
Cancer stage		
II	3	5.2
III	7	12.1
IVA	41	70.7
IVB	7	12.1
T stage		
T1	2	3.5
T2	16	27.6
T3	9	15.5
T4	31	53.4
N stage		
N0	15	25.9
N1	8	13.8
N2	32	55.1
N3	3	5.2
Chemotherapy		
Yes	33	56.9
No	25	43.1
Surgery		
Yes	15	25.9
No	43	74.1
RT technique		
Conventional	29	50.0
IMRT	29	50.0
Smoking status*		
Yes	43	74.1
No	9	15.5
Unknown	6	10.3
Number of pack-years (n = 43)		
<10	39	90.7
>10	4	9.3

IMRT: Intensity modulated radiotherapy; RT: Radiotherapy
*Inclusive of current and ex-smoker.

5 patients proceeded to salvage surgery. One of these 5 patients underwent a salvage neck dissection for isolated nodal recurrence and has subsequently remained disease-free from hypopharyngeal carcinoma, although he died at 20 months post-RT from a second primary lung cancer. The rest of the patients died of disease recurrence despite salvage surgery.

Patterns of Failure

Median follow-up was 15.9 months for all patients. In those alive, the median follow-up was 21.7 months (range:

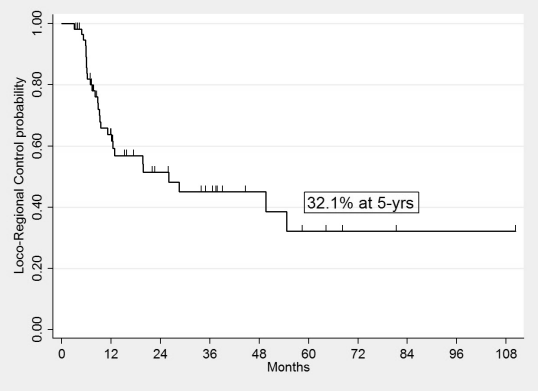

Fig. 1. Loco-regional control (LRC) of hypopharyngeal cancer following RT.

Table 2. Univariate Analysis of Patients with Hypopharyngeal Cancer

Variable	Overall Survival (OS)		Loco-Regional Control (LRC)		Progression-Free Survival (PFS)	
	Hazard Ratio (95% CI)	*P* Value†	Hazard Ratio (95% CI)	*P* Value†	Hazard Ratio (95% CI)	*P* Value†
Age, years						
Per year increase	0.99 (0.96 – 1.03)	0.629	0.99 (0.95 – 1.04)	0.775	1.00 (0.96 – 1.04)	0.915
Gender						
Male	2.35 (0.71 – 7.83)		0.62 (0.21 – 1.82)		0.88 (0.31 – 2.53)	
Female	1	0.163	1	0.387	1	0.818
Chemotherapy						
Yes	0.82 (0.44 – 1.53)		0.75 (0.36 – 1.57)		0.87 (0.45 – 1.66)	
No	1	0.530	1	0.443	1	0.669
Subsite						
Pyriform fossa	1.09 (0.59 – 2.00)		0.75 (0.35 – 1.58)		0.87 (0.45 – 1.67)	
Others	1	0.793	1	0.448	1	0.677
RT technique						
IMRT	0.52 (0.20 – 1.35)		0.59 (0.18 – 1.97)		0.57 (0.20 – 1.63)	
2D	1	0.18	1	0.391	1	0.297
Smoking status‡						
Yes	0.86 (0.33 – 2.24)		0.59 (0.20 – 1.75)		0.61 (0.23 – 1.59)	
No	1	0.764	1	0.343	1	0.313
T stage						
T1– T2	0.46 (0.22 – 0.96)		0.40 (0.16 – 0.99)		0.28 (0.12 – 0.69)	
T3 – T4	1	0.040*	1	0.049*	1	0.005*
N stage						
N0 – N1	0.66 (0.35 – 1.28)		0.57 (0.25 – 1.27)		0.56 (0.28 – 1.13)	
N2 – N3	1	0.220	1	0.166	1	0.104
Group stage						
IVA – IVB	2.36 (0.92 – 6.05)		2.73 (0.81 – 9.14)		3.69 (1.12 – 12.10)	
II – III	1	0.075	1	0.104	1	0.032*
Surgery						
No	1.09 (0.53 – 2.23)		3.24 (0.97 – 10.79)		1.41 (0.64 – 3.09)	
Yes	1	0.818	1	0.055	1	0.396

IMRT: Intensity modulated radiotherapy; RT: Radiotherapy; 2D: 2-dimensional

*P value <0.05 is statistically significant.

†P value is based on Cox-proportional hazard.

‡Patients with unknown smoking status were excluded from the analysis.

6.6 to 81.1 months). The median LRC was 26 months with a 3-year LRC rate of 45% (95% CI, 29.6% to 59.2%) (Fig. 1). Local recurrence was observed in 12 patients, whereas 2 patients developed regional recurrence and 14 patients had both local and regional recurrence. The overall incidence of distant metastasis was 36.2% (n = 21). The lung was the most frequent site of distant metastasis (76.2%). The 3-year distant recurrence-free survival rate was 58.2% (95% CI, 41% to 72%). In univariate analysis, T stage was the only significant predictor found for LRC ($P = 0.049$) with a hazard ratio (HR) of 0.40 (95% CI, 0.16 to 0.99) of T1/T2 against T3/T4 as reference (Table 2).

Survival

Forty-three patients died over the study period and the cause of death was cancer-related in most of the patients (35/43). Of the others who died, 6 patients died from pneumonia, 1 patient died from a second esophageal primary, 1 patient died from a second lung primary. At the time of analysis, 15 patients were alive and 14 of them were disease-free at the last follow-up. The median OS was 21.0 months with a 3-year OS rate of 33.5% (95% CI, 20.8% to 46.7%) (Fig. 2). The median PFS was 12.8 months with a 3-year PFS rate of 34.9% (95% CI, 22% to 48.2%) (Fig. 3). Univariate analysis showed that T stage was the only significant prognostic factor for OS. Group stage and T stage were respectively significant univariate prognostic factors for PFS. In a multivariate analysis, only T stage was significant with T1/T2 showing a HR of 0.28 (95% CI, 0.12 to 0.69, $P = 0.005$) vs T3/T4 (Table 2).

Discussion

Our study results demonstrated the poor outcome expected in hypopharyngeal carcinoma with 3-year OS of 33.5% and LRC of 45%. The majority of patients (83%) in our cohort presented with very advanced stage (stages IVA & IVB). Although 88% of patients managed to achieve complete response 3 months after completion of treatment, loco-regional recurrence remained the major cause of failure following curative intent RT. Most deaths occurred in patients who succumbed to loco-regional rather than systemic failure.

Our centre has increasingly employed IMRT in the last decade for the definitive treatment of head and neck cancer. The use of IMRT has allowed the delivery of high dose conformal RT whilst achieving normal tissue tolerances. The earlier group of patients in our study was treated with 2D RT and the latter half received IMRT. On univariate analysis, the use of IMRT was not found to be a statistically significant prognostic factor affecting OS, PFS and LRC compared to conventional RT. However, the small number of patients and significant shorter follow-up period of IMRT patients (median follow-up: 12.0 months in IMRT group vs 22.4 months in 2D group) may have accounted for this finding.

Few studies have reported the outcomes of IMRT due to the relative rarity of hypopharyngeal cancer. Mok et al[8] compared 3-dimensional (3D) RT and IMRT in 181 patients with hypopharyngeal squamous cell carcinoma (SCC), 40% of which had T1/T2 stage. The IMRT group had a higher 3-year LRC (75% vs 58%) compared with the 3D RT group, but both groups had similar OS (50% vs 52%) and distant relapse rate. Huang et al[9] reported the results of 47 hypopharyngeal patients treated with concomitant IMRT-chemotherapy, although 30% of these patients were treated in the adjuvant setting. After a relatively short median follow-up of 18.8 months, the 5-year OS for all patients was 37% and the 5-year LRC in the concomitant CRT group was 53%. Longer follow-up and bigger cohort of patients are needed to validate these IMRT findings with regard to control rates and toxicities.

These results provide a clear rationale for efforts aimed at improving LRC and OS. Strategies that are being explored include altered fractionation, use of conformal RT

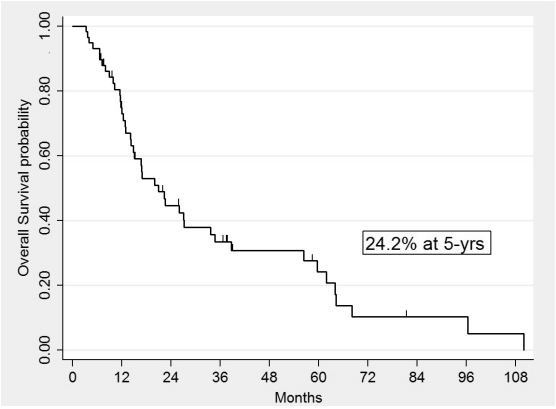

Fig. 2. Overall survival (OS) of hypopharyngeal cancer patients following RT.

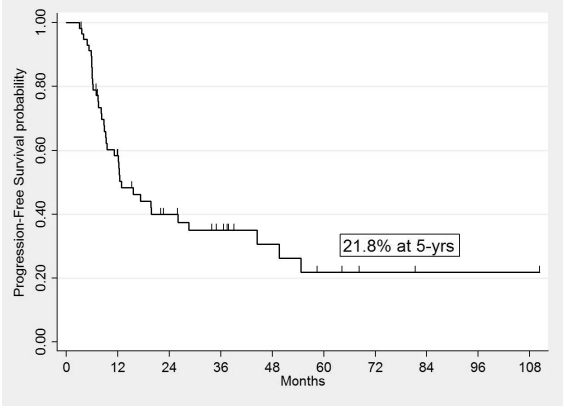

Fig. 3. Progression-free survival (PFS) of hypopharyngeal cancer following RT.

such as IMRT, and intensification of concurrent systemic chemotherapy. Several reports have shown improvement in LRC and a small benefit of OS with altered fractionation, often at the price of significant morbidities.[10,11] Gujraj et al reported the long-term outcome of a phase I/II accelerated RT study of dose-escalated IMRT for locally advanced laryngo-hypopharyngeal cancers.[12,13] This study demonstrated that dose-escalated IMRT at 67.2 Gy in 28# (2.4 Gy per fraction) to PTV1 and 56 Gy in 28# (2 Gy per fraction) to PTV2 resulted in 5-year local control rate of 75% and 5-year OS of 67.6% with acceptable late toxicity. This dose level is currently being investigated in the context of a randomised controlled trial (ART-DECO) in the United Kingdom.

Significant advances have been made over the last 2 decades with the development of more complex RT delivery techniques such as IMRT, volumetric modulated arc therapy (VMAT), and proton therapy. The increasing incorporation of newer imaging modalities such as MRI and positron emission tomography (PET) also allows for more precise staging, tumour localisation and assessment of treatment response. There is also ongoing interest and research to investigate the role of imaging to improve target delineation and possibly identify areas of radio-resistance within the tumour for dose painting/escalation.[14] Further clinical research is needed to assess the utilisation of newer highly conformal RT techniques combined with novel systemic agents in head and neck cancers.

Conclusion

Patients with hypopharyngeal cancers often presented with advanced stage with extensive nodal involvement and were at high risk of developing distant metastasis. Tumour load is the most important prognostic factor for outcome. Intensification of treatment is warranted to enhance local control and OS rates.

REFERENCES

1. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685.
2. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890.
3. Lefebvre JL, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L, et al. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 2012;23:2708.
4. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol 2013;31:845-52.
5. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-8.
6. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
7. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100:33.
8. Mok G, Gauthier I, Jiang H, Huang SH, Chan K, Witterick IJ, et al. Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck 2015;37:655-61.
9. Huang WY, Jen YM, Chen CM, Su YF, Lin CS, Lin YS, et al. Intensity modulated radiotherapy with concurrent chemotherapy for larynx preservation of advanced resectable hypopharyngeal cancer. Radiat Oncol 2010;5:37.
10. Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys 2014;89:13-20.
11. Bernier J. Alteration of radiotherapy fractionation and concurrent chemotherapy: a new frontier in head and neck oncology? Nat Clin Pract Oncol 2005;2:305-14.
12. Gujral DM, Miah AB, Bodla S, Richards TM, Welsh L, Schick U, et al. Final long-term results of a phase I/II study of dose-escalated intensity-modulated radiotherapy for locally advanced laryngo-hypopharyngeal cancers. Oral Oncol 2014;50:1089-97.
13. Miah AB, Bhide SA, Guerrero-Urbano MT, Clark C, Bidmead AM, St Rose S, et al. Dose-escalated intensity-modulated radiotherapy is feasible and may improve locoregional control and laryngeal preservation in laryngo-hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2012;82:539-47.
14. Grosu AL, Souvatzoglou M, Roper B, Dobritz M, Wiedenmann N, Jacob V, et al. Hypoxia imaging with FAZA-PET and theoretical considerations with regard to dose painting for individualiza- tion of radiotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:541-51.

Kiattisa Sommat, [1]*MRCP, FRCR*, Sook Kwin Yong,[2]*MPH*, Kam Weng Fong, [1]*FRCR*, Terence WK Tan, [1]*FRCR*, Joseph TS Wee, [1]*FRCR*, Yoke Lim Soong, [1]*FRCR*

[1]Division of Radiation Oncology, National Cancer Centre Singapore, Singapore
[2]Division of Clinical Trial and Epidemiological Sciences, National Cancer Centre Singapore, Singapore

Address for Correspondence: Dr Kiattisa Sommat, Division of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: kiattisa.sommat@singhealth.com.sg

Confluent Atypical Molluscum Contagiosum Causing Disfigurement in a Human Immunodeficiency Virus Patient

Dear Editor,

Molluscum contagiosum (MC) is a viral disease caused by molluscipoxvirus. The first peak incidence occurs in preschool children. A second peak incidence occurs in young adults in which the condition is generally considered to be a sexually transmitted disease. Though the disease is self-limiting and the lesions are usually small, discrete, pearly and dome-shaped with central umbilication, atypical and rare varieties could be found in some patients, in which the lesions may be large, confluent or non-umbilicated.

Case Report

A 60-year-old male patient presented to our department with complaints of painless multiple flesh-coloured papules and plaques on his body. They were located primarily on the eyelids, forehead, neck and extremities. Two years ago, he had numerous small, waxy, non-tender papules scattered all over his face and was misdiagnosed with vulvar syringomas, receiving laser treatment. In the following 2 months, the lesions increased gradually and had spread to the face, neck and extremities. Numerous papules on his eyelids were large, coalescent and had joined together to form an enlarged structure of more than 3 cm in length, producing a unique appearance. As a result, his eyes could not fully open (Fig. 1). Small multiple lesions were non-tender with shiny skin nodules of up to 0.5 cm in diameter covering his face, neck and extremities, but these were less confluent.

Biopsy was taken from a nodule on the left eyelid. Histopathologic examination with haematoxylin and eosin (H&E) staining revealed a hypertrophied and hyperplastic epidermis. Above the basal layer, enlarged cells containing large intracytoplasmic inclusions suggestive of Henderson-Patterson bodies were indentified (Fig. 2). On investigation, the patient tested positive for human immunodeficiency virus (HIV) on the ELISA test. His white blood cell count was 3.64 $\times 10^9$/L with hypochromic and microcytic blood picture. The CD4 cell was 141 (9%). Total serum IgG concentration was 24.9 g/L, IgA 14.2 g/L, IgM 2.67 g/L.

Discussion

MC is a common benign, often self-limiting, cutaneous disease resulting from poxvirus infection. It often occurs

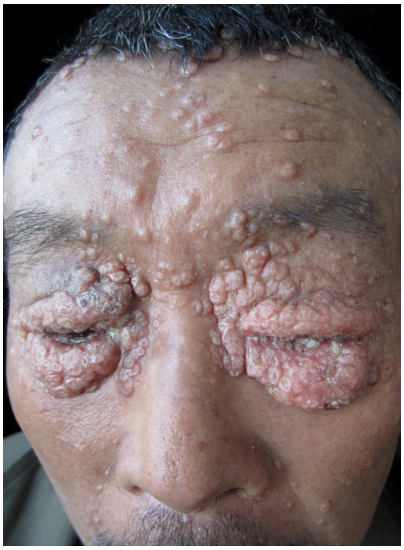

Fig. 1. Confluent molluscum lesions that covered the patient's eyelids, contributing to his disfigurement.

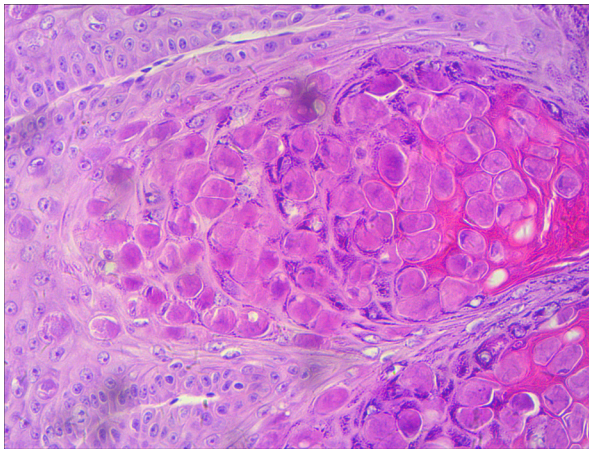

Fig. 2. Higher magnification showing intracytoplasmic eosinophilic structures – the so-called molluscum bodies (H&E stain x 400 magnification).

in children, sexually active adults and immunosuppressed patients, especially those with HIV infection. In HIV-positive patients, MC tends to occur during the advanced phase of the disease and signifies advancing immunosuppression. In one study, the prevalence of mucocutaneous findings in HIV-positive children with severe, moderate or no evidence of immunosupression was 62%,43% and 20%, respectively.[1] Among persons infected with HIV, the prevalence of MC has been reported to range from 5% to 18%,[2-4] and is thought to be a clinical sign of marked HIV progression and very low CD4 cell counts. A study by Koopman et al[5] on 72 patients with HIV reports on the prevalence of MC lesions in these patients and found that as many as 33.3% of them had low CD4 counts (below 100×10^6/L). In another study of 27 patients with HIV infection, the mean CD4 count was 86×10^6/L.[6] There was also a statistically significant correlation between the CD4 cell count and extent of MC infection.[6,7] Perez-Blazquez et al[8] have proposed that in advanced HIV infection, MC lesions of the eyelid occur when the CD4 cell count lies below 80 cells/uL.

Classical lesions of MC are discrete, dome-shaped, umblicated and waxy papules that are either skin-coloured or white. Lesions are usually distributed on the axillae, lower abdomen, sides of trunk, thighs and face. Uncommon sites include scalp, lips, tongue, buccal mucosa membrane, soles and eyelids. MC infection in HIV patients may present with pearly skin-coloured umblicated papules. MC lesions that occur in acquired immune deficiency syndrome (AIDS) patients differ in size, site and morphology from those occuring in the immunocompetent. Lesions may resemble comedones, abscesses, furuncles, condylomas, syringomas, keratoacanthomas, ecthyma, sebaceous nevus, or cutaneous horn.[9] Of importance is that disseminated fungal infections (specifically, cryptococcosis), *Penicillium marneffei* infection and histoplasmosis are reported to clinically mimic MC[10,11] and can also coexist in the same lesion.[12] Because of the atypical nature of molluscum in HIV-positive patients, diagnosis depends largely on biopsy.

In this case report, the morphology of the facial lesions was not immediately suggestive of MC. Complicating the diagnostic picture were the size, site and absence of a central umbilication. Although many studies state that HIV-infected patients may show MC all over the body, few cases show the atypical forms such as those found in this report.[13] On biopsy, it was found that the patient had MC virus infection. Histopathological examination of the specimen from the skin lesions had played a crucial role in the diagnosis.

Conclusion

For clinically atypical lesions, a diagnosis of MC should be considered and these cases should be tested for biopsy in order to avoid misdiagnosis and guard against AIDS.

REFERENCES

1. Wananukul S, Deekajorndech T, Panchareon C, Thisyakorn U. Mucocutaneous findings in pediatric AIDS related to degree of immunosuppression. Pediatr Dermatol 2003;20:289-94.
2. Goodman DS, Teplitz ED, Wishner A, Klein RS, Burk PG, Hershenbaum E. Prevalence of cutaneous disease in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex. J Am Acad Dermatol 1987;17:210-20.
3. Coldiron BM, Bergstresser PR. Prevalence and clinical spectrum of skin disease in patients infected with human immunodeficiency virus. Arch Dermatol 1989;125:357-61.
4. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med 1993;328:1670-4.
5. Koopman RJ, van Merriënboer FC, Vreden SG, Dolmans WM. Molluscum contagiosum; a marker for advanced HIV infection. Br J Dermatol 1992;126:528-9.
6. Schwartz JJ, Myskowski PL. Molluscum contagiosum in patients with human immunodeficiency virus infection. A review of twenty-seven patients. J Am Acad Dermatol 1992;27:583-8.
7. Goldstein B, Berman B, Sukenik E, Frankel SJ. Correlation of skin disorders with CD4 lymphocyte counts in patients with HIV/AIDS. J Am Acad Dermatol 1997;36:262-4.
8. Pérez-Blázquez E, Villafruela I, Madero S. Eyelid molluscum contagiosum in patients with human immunodeficiency virus infection. Orbit 1999;18:75-81.
9. Czelusta A, Yen-Moore A, Van der Straten M, Carrasco D, Tyring SK. An overview of sexually transmitted diseases. Part III. Sexually transmitted diseases in HIV-infected patients. J Am Acad Dermatol 2000;43:409-32.
10. Ghigliotti G, Carrega G, Farris A, Burroni A, Nigro A, Pagano G, et al. Cutaneous cryptococcosis resembling molluscum contagiosum in a homosexual man with AIDS. Report of a case and review of the literature. Acta Derm Venereol 1992;72:182-4.
11. Ramdial PK, Calonje E, Sing Y, Chotey NA, Aboobaker J. Molluscum-like cutaneous cryptococcosis: a histopathological and pathogenetic appraisal. J Cutan Pathol 2008;35:1007-13.
12. Annam V, Inamadar AC, Palit A, Yelikar BR. Co-infection of molluscum contagiosum virus and cryptococcosis in the same skin lesion in a HIV-infected patient. J Cutan Pathol 2008;35:29-31.
13. Itin PH, Gilli L. Molluscum contagiosum mimicking sebaceous nevus of Jadasson, ecthyma and giant condylomata acuminata in HIV-infected patients.Dermatology 1994;189:396-8.

Guang Wen Yin, [1]*MD*, Jing Li, [1]*MM*

[1]Department of Dermatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou City, Henan Province, People's Republic of China

Address for Correspondence: Dr Yin Guang Wen, Department of Dermatology, The First Affiliated Hospital of Zhengzhou University, No. 1, East Jianshe Road, Zhengzhou City, 450052, Henan Province, People's Republic of China.
Email: gwyin67@126.com.cn

Alternative Strategies for Central Venous Stenosis and Occlusion in Patients Requiring Haemodialysis Access

Dear Editor,

The use of tunnelled dialysis catheters (TDCs) in patients awaiting permanent dialysis access creation has resulted in a rise in the prevalence of central venous stenosis and occlusion (CVSO) in up to 50% of cases.[1,2]

CVSO is a difficult problem to manage. The mainstay of treatment for CVSO includes percutaneous transluminal angioplasty (PTA) and stenting. These are, however, prone to recurrence, with primary patency rates of not more than 50% at 1 year.[3-6] Potential long-term complications of CVSO include venous hypertension leading to recirculation and failure of vascular access, symptomatic limb swelling, and superior vena cava syndrome. Alternative vascular access techniques such as lower extremity arteriovenous grafts (AVGs) have high infection rates (27%), limited patency and are associated with other morbidities such as lower limb ischaemia.[7,8]

Two novel hybrid surgical options have been described in literature, but are rarely used in the local setting. The Haemodialysis Reliable Outflow (HeRO) graft circumvents the site of central obstruction, while the GORE® hybrid vascular graft allows deployment of an integrated stent to treat the stenotic central vein. Multicentre studies on the HeRO graft have shown superior patency (88% vs 37%) and infection rates (0.14 vs 2.3 infection/1000 days) when compared with TDC, and similar patency rates with conventional AVG (90% vs 65%).[9,10]

We introduce the first 2 local patients receiving the aforementioned vascular grafts and discuss these alternative options for patients with CVSO.

Case 1

A 45-year-old male became dialysis-dependent in 2006 and underwent multiple upper limb arteriovenous fistulas (AVF) from 2006 to 2011, all of which ultimately failed. He required a total of 4 TDCs for temporisation of access during this period. This resulted in bilateral jugular and subclavian vein occlusions with multiple tortuous collateral veins draining into the superior vena cava (Fig. 1A). He was deemed not a candidate for further upper extremity haemodialysis access until 2015 when the HeRO graft became available in Singapore.

A left upper limb HeRO graft was subsequently inserted. Ultrasound-guided percutaneous access of a collateral vein was performed, followed by advancement of a guide wire and 4 Fr micropuncture catheter. Direct injection of contrast was used for roadmap fluoroscopy and guidance of wire and catheter into the left brachiocephalic vein (Fig. 1B). The catheter was then exchanged for an 8 Fr sheath prior to deployment of the catheter portion of the HeRO graft in the superior vena caval-atrial junction (Fig. 1C). He had an uneventful recovery and was discharged home the following day.

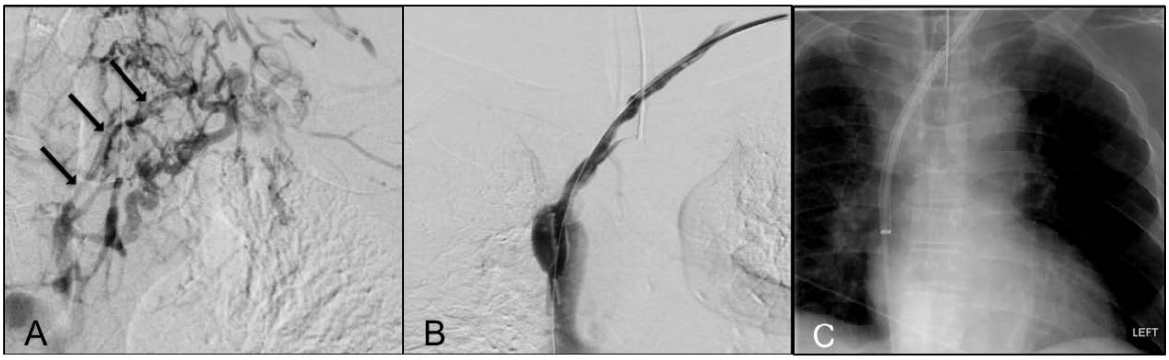

Fig 1. (A) Multiple well formed collaterals. Arrows showing the vein that was accessed for TDC and subsequently HeRO graft insertion. (B) Angiogram of collateral vein accessed. (C) HeRO graft advanced to the junction of superior vena cava and right atrium.

Case 2

A 56-year-old female initiated haemodialysis in 2013. She subsequently underwent a series of failed left upper limb AVFs and an AVG. This was followed by recurrent left brachiocephalic vein occlusions (Fig. 2A) and thrombosis of the AV graft, for which thrombectomy attempts were unsuccessful due to poor central venous outflow. She required 3 TDC insertions during this time.

A left upper limb GORE® hybrid vascular graft was tunnelled subcutaneously and inserted via the left subclavian vein. The integrated stent was deployed in the brachiocephalic vein to treat the area of stenosis (Fig. 2B). She was discharged well on postoperative day 3.

Both grafts were anastomosed to the ipsilateral brachial artery distally. They underwent successful haemodialysis through the subcutaneous grafts from 2 weeks after insertion. No immediate or medium-term complications were reported to date (1-year post implant).

Discussion

End-stage renal disease is increasing over the past decade, resulting in a rise in patients requiring haemodialysis. The Singapore Renal Registry reported increased prevalence of chronic kidney disease stage 5 (CKD5) from 2466 patients in 1999 to 5912 patients in 2014. The vast majority of CKD5 patients (88.4%) underwent haemodialysis, making this population group vulnerable to potential complications of CVSO.

CVSO remains a significant problem in patients requiring vascular access for haemodialysis, and is mainly attributed to prior central venous catheter placements.[1,11] Up to 41% of patients presenting with vascular access-related issues have evidence of significant CVSO on venogram.[1]

The mainstay of treatment is currently limited to endovascular options. PTA remains the simpler approach, but with a reported 12-month primary patency rates ranging from 12% to 50%.[3-5,12] Bare metal and covered stenting have shown to improve initial patency rates, but are associated with risks of migration, fracture, in-stent stenosis, and ultimately occlusion.[3]

The HeRO graft comprises 3 components (Fig. 3A): First, a nitinol-reinforced venous outflow component is tunnelled subcutaneously, entering the right atrium via the subclavian or internal jugular vein. This is connected by a titanium connector to an expanded polytetrafluoroethylene (ePTFE) AVG, completing the 3-component device (venous outflow component, titanium connector and ePTFE AVG). This is then tunnelled subcutaneously and anastomosed to the ipsilateral brachial artery. A 4-centre review showed primary and secondary patency rates of 48.8% and 90.8%, respectively, at 1-year, with access-related infection rates of 0.14 per 1000 days.

The GORE® hybrid vascular graft (Fig. 3B) is an ePTFE AVG with a nitinol covered stent at the venous outflow section. The luminal surface of the hybrid graft and stent is bonded with a bioactive substance consisting of reduced-molecular-weight heparin to prevent thrombosis. An integrated stent addresses the outflow stenosis, potentially improving re-intervention rates.[13,14] Initial published

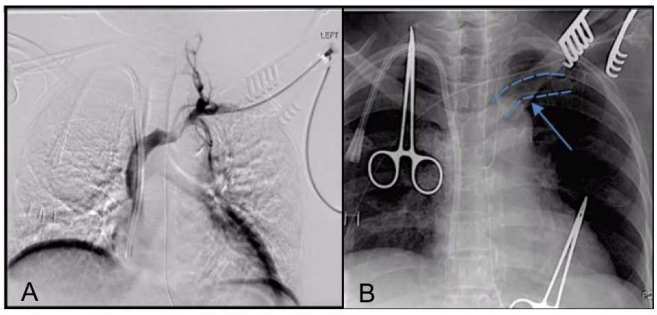

Fig 2. (A) Preoperative central venogram showing stenosis of the left brachiocephalic vein. (B) Stent deployed in the left brachiocephalic vein (outline indicated by arrow).

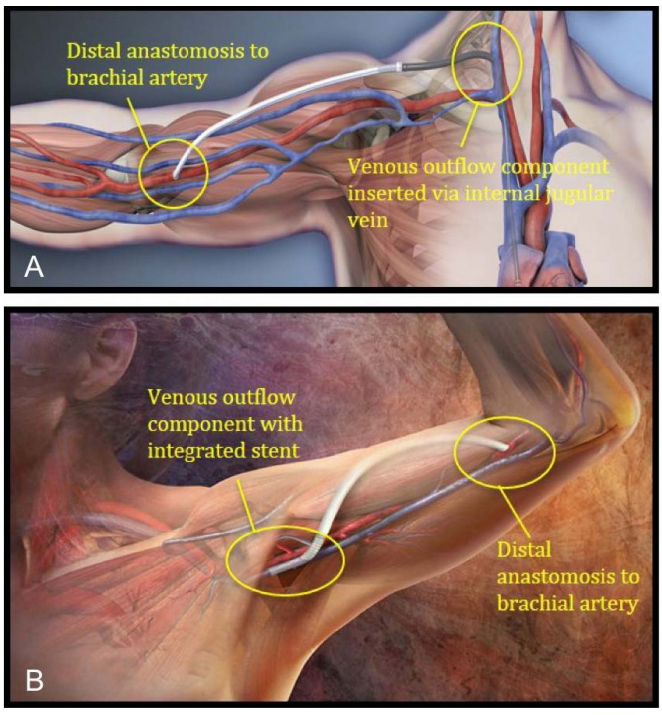

Fig 3. (A) Haemodialysis Reliable Outflow (HeRO) graft comprising 3 components – a nitinol-reinforced venous outflow component, a titanium connector, and an ePTFE AVG. (B) GORE® hybrid vascular graft – an ePTFE AVG with an integrated nitinol covered stent at the venous outflow section.

experiences have shown promising benefits, with no reported problems locally or internationally.

Conclusion

The HeRO graft and GORE® hybrid vascular graft are 2 novel alternatives that can be safely considered in patients who have exhausted conventional means to attain haemodialysis access. The former circumvents the CVSO in more proximal or extensive lesions up to the right atrium, while the latter allows deployment of an integrated stent to treat an area of central venous stenosis. Patients who were previously considered to have exhausted all upper extremity haemodialysis vascular access may yet have 1 or 2 more options with these newer treatment modalities.

REFERENCES

1. MacRae JM, Ahmed A, Johnson N, Levin A, Kiaii M. Central vein stenosis: a common problem in patients on hemodialysis. ASAIO J 2005;51:77-81.
2. Agarwal AK, Patel BM, Haddad NJ. Central vein stenosis: a nephrologist's perspective. Semin Dial 2007;20:53-62.
3. Kundu S. Central venous obstruction management. Semin Intervent Radiol 2009;26:115-21.
4. Shi YX, Ye M, Liang W, Zhang H, Zhao YP, Zhang JW. Endovascular treatment of central venous stenosis and obstruction in hemodialysis patients. Chin Med J (Engl) 2013;126:426-30.
5. Bakken AM, Protack CD, Saad WE, Lee DE, Waldman DL, Davies MG. Long-term outcomes of primary angioplasty and primary stenting of central venous stenosis in hemodialysis patients. J Vasc Surg 2007;45:776-83.
6. Thwaites S, Robless PA. Central vein stenosis in an Asian hemodialysis population. Asian Cardiovasc Thorac Ann 2012;20:560-5.
7. Geenen IL, Nyilas L, Stephen MS, Makeham V, White GH, Verran DJ. Prosthetic lower extremity hemodialysis access grafts have satisfactory patency despite a high incidence of infection. J Vasc Surg 2010;52:1546-50.
8. Harish A, Allon M. Arteriovenous graft infection: a comparison of thigh and upper extremity grafts. Clin J Am Soc Nephrol 2011;6:1739-43.
9. Gage SM, Katzman HE, Ross JR, Hohmann SE, Sharpe CA, Butterly DW, et al. Multi-center experience of 164 consecutive Hemodialysis Reliable Outflow [HeRO] graft implants for hemodialysis treatment. Eur J Vasc Endovasc Surg 2012;44:93-9.
10. Katzman HE, McLafferty RB, Ross JR, Glickman MH, Peden EK, Lawson JH. Initial experience and outcome of a new hemodialysis access device for catheter dependent patients. J Vasc Surg 2009;50:600-7.
11. Schillinger F, Schillinger D, Montagnac R, Milcent T. Post catheterisation vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses. Nephrol Dial Transplant 1991;6:722-4.
12. Kovalik EC, Newman GE, Suhocki P, Knelson M, Schwab SJ. Correction of central venous stenoses: use of angioplasty and vascular Wallstents. Kidney Int 1994;45:1177-81.
13. Ross JR. Percutaneous venous anastomosis with a hybrid vascular graft. Available at: http://evtoday.com/2012/06/percutaneous-venous-anastomosis-with-a-hybrid-vascular-graft/. Accessed on 1 February 2016.
14. Kakisis JD, Avgerinos E, Giannakopoulos T, Moulakakis K, Papapetrou A, Liapis CD. Balloon angioplasty vs nitinol stent placement in the treatment of venous anastomotic stenoses of hemodialysis grafts after surgical thrombectomy. J Vasc Surg 2012;55:472-8.

Keith Koh, [1]*MBBS (Aus), MRCS (Edin)*, Ye Xin Koh, [1]*MBBS (S'pore), MRCS (Edin)*, Edward TC Choke, [2]*MBBS (Hons), PhD (London), FRCS (UK)*, John CC Wang, [2]*MBBCh BAO, LRCPI & SI, MSc*, Ch'ng Jack Kian, [2]*MBBCh BAO, LRCP & SI (NUI), FRCS*

[1]Department of General Surgery, Singapore General Hospital, Singapore
[2]Department of Vascular Surgery, Singapore General Hospital, Singapore

Address for Correspondence: Dr Keith Koh, 70B Telok Blangah Heights, #10-525, Singapore 102070.
Email: Keith.koh@mohh.com.sg