



AAMS

Annals of the Academy of Medicine, Singapore

MCI(P) 004/11/2013

VOLUME 43

NUMBER 10

FREE PAPERS

OCTOBER 2014



Reproduced with permission from:
Pearl Gan

"The vision must be followed by the venture. It is not enough to stare up the steps—we must step up the stairs."

Vance Havner (1901 –)
American clergyman

CONTENTS

Editorial

- 481 **Staying Relevant with the Times—The Changing Face of an Asylum**
Siow Ann [Chong](#), Aditya [Subramaniam](#)

Original Articles

- 484 **Assessment of the American Joint Committee on Cancer 7th Edition Staging for Localised Prostate Cancer in Asia Treated with External Beam Radiotherapy**
Meihua [Wong](#), Connie [Yip](#), Huihua [Li](#), et al
- 492 **Changes in Mechanical, Structural Integrity and Microbiological Properties Following Cryopreservation of Human Cadaveric Iliac Arteries**
Stephen KY [Chang](#), Joel WL [Lau](#), Chee Kong [Chui](#)
- 499 **Biological Reconstruction for Children with Osteosarcoma Around the Knee**
Mark E [Puhaindran](#), Robert WH [Pho](#)
- 506 **Natural History and Comorbidities of Subjects with Subclinical Hyperthyroidism: Analysis at a Tertiary Hospital Setting**
Shaikh Abdul Kader Kamaldeen [Abdul Shakoor](#), et al
- 511 **A Double-Blind, Randomised, Placebo-Controlled Trial of EMLA® Cream (Eutectic Lidocaine/Prilocaine Cream) for Analgesia Prior to Cryotherapy of Plantar Warts in Adults**
Siew Hui [Lee](#), Janthorn [Pakdeethai](#), et al

Please see inside Contents for the full list of articles.

Staying Relevant With the Times—The Changing Face of an Asylum

Siow Ann Chong,¹ MBBS, MMed (Psychiatry), MD, Aditya Subramaniam,²

Last year, the Institute of Mental Health (IMH) celebrated its 85th anniversary. From its origins in 1928 as what was then simply called The Mental Hospital, this nondescript name was later changed in 1950 to Woodbridge Hospital.¹

The establishment of the Mental Hospital was at a time when there was no effective treatment for mental illness. The only humane option at the time was “moral treatment”, which meant kind, individualised treatment in the form of occupational therapy, exercise, and recreation in a sheltered environment. The hospital was, in fact, an asylum in the original meaning of the word: “a refuge, protection, or sanctuary”.

This humane idea of looking after the mentally ill reached its apotheosis in America when the early mental hospitals built in the 19th century took the form of large, stately buildings, with large sprawling grounds and comfortable accommodation that also created a sense of community and companionship for the patients. There were farms and dairies that provided therapy for the patients in the form of work, and these agricultural activities also helped to sustain the running of the hospitals.

Antipsychiatry Movement

However, it was also in America where the page turned with the precipitate decline of this high-minded ideal. An influx of an increasing number of patients and shortage of funds strained these mental hospitals to their limits and forced them to closure. Within a few decades, most morphed into “warehouses” for the mentally ill, and became synonymous with neglect, misery and abuse.

Journalistic exposé of the appalling conditions of these hospitals whipped up a sense of public revulsion and outrage, which was further stoked by Ken Kesey’s novel ‘One Flew Over the Cuckoo’s Nest’ and the subsequent blockbuster movie with its graphic depiction of the sequential brutalisation of a wayward patient at the hands of the staff of a mental hospital.

As described by the historian Edward Shorter, there was a time in the early 1960s that, in an almost concerted move in certain intellectual circles, a series of influential books were published, speaking against the practice of psychiatry.² Sociologist Erving Goffman’s ‘Asylums’, portrayed asylums as “total institutions”, that deprived patients of their autonomy, imposing rigid rules that further humiliated and constrained them, creating a gulf between staff and patients. Michael Foucault’s ‘Madness and Civilization’ argued that the notion of mental illness was a social and cultural invention. Thomas Szasz’s book, ‘The Myth of Mental Illness’, called the whole notion of psychiatric illness “scientifically worthless and socially harmful”, and that mental illness was simply a myth. In the United Kingdom, Ronald D Laing’s ‘The Divided Self’ presented schizophrenia as a rational response to intolerable experiences and argued the psychotic symptoms were assumed to “throw dangerous people off the scent.” The gist of their collective arguments which fueled the antipsychiatry movement was that mental illness is not medical in nature and that it does not exist other than as social, political, and legal constructs deployed to exert control over certain members of society.

Deinstitutionalisation

What initiated the subsequent massive closing down of mental hospitals and the exodus of patients to the community, a process known as deinstitutionalisation, was the increasingly strident and vociferous antipsychiatry movement, and the discovery of antipsychotic drugs in the 1950s, which greatly ameliorated the disruptive behaviour of patients and held the promise of returning patients back to their families and communities.

In theory, deinstitutionalisation is the transfer of care of mentally ill patients from these long-stay mental hospitals to smaller community-based alternatives.³ It also requires the shunting of potential new admissions to these mental

¹Research Division, Institute of Mental Health, Singapore

²Boston University, United States of America

Address for Correspondence: Prof Chong Siow Ann, Research Division, Institute of Mental Health, Buangkok Green Medical Park, 10 Buangkok View, Singapore 539747.

Email: siow_ann_chong@imh.com.sg

hospitals to alternative facilities, and the development and installation of special services in the community for the care of these patients.⁴

It was also widely assumed that community-based care would be more humane, therapeutic, and cost effective.⁴⁻⁶ But in practice and in reality, things did not work out that way. The communities were ill-prepared and ill-equipped to receive and support the burgeoning number of discharged patients. Many of these patients had been institutionalised for such a long time and had become so accustomed to a highly structured and sheltered living environment that they were incapable of independent living outside the hospital.⁷ These hastily discharged patients, bereft of shelter, became homeless, and in full view of an intolerant and fearful public, were often picked up by the police. Many landed in prisons rather than in hospitals, resulting in what was subsequently called “a criminalisation of mentally disordered behaviour” which is the diversion of mentally ill persons who need treatment into the criminal justice system instead of the mental health system.⁸

Perhaps the American experience with deinstitutionalisation held some salutary lessons for us, for there was no parallel massive deinstitutionalisation in Singapore, and perhaps, the time for it was not right. In a somewhat contrarian move, the foundation was laid for a new and bigger mental health facility in 1988, which in 1993, became the present IMH and the old Woodbridge Hospital was eventually torn down.

With better knowledge, experience, and with some advances in treatment (both pharmacological and psychosocial), as well as a change in the way mental health and mental illnesses are viewed by the public and policy makers, there is now the political commitment to further develop and expand the community treatment of the mentally ill. These include early detection mechanisms, with involvement of the primary healthcare sector and other community care providers, which could have the potential to attain recovery and preservation of mental function, even for those with serious mental illness, and prevent the deterioration to that state when institutionalised care is needed.

In 2007, Singapore implemented the first National Mental Health Policy and Blueprint to promote mental health, and restructure the delivery of mental health care in all the sectors and levels—from the hospitals to the community. We are now in the second phase of our National Mental Health Blueprint and an important component of which is to further develop the range of services across the various healthcare and social sectors for community healthcare. The IMH is also striving to reduce its large population of patients who have been long institutionalised. This is well and good, but despite what we do, there are limits.

We hear often that plaintive question asked by elderly parents of what would happen when they are no longer able to look after their mentally disabled offspring; we hear this from any despairing caregiver who has reached the end of his or her tether as well. As a result of the incomplete knowledge and the limitations of our current treatments despite the advances in the last few decades, and because many mental illnesses are still not detected early, there will always be a group of patients, including those with severe intractable, disruptive, and potentially dangerous behaviour, who need highly structured and secure 24-hour care and those who are not dangerous but need close nursing. These patients and their exhausted caregivers have few resources. Economically depleted and stigmatised, isolated and defranchised, they lack the means to get the basic necessities including food, shelter, medical care, and social support.

In an essay, ‘The Lost Virtues of the Asylum’, the neurologist and writer Oliver Sacks,⁹ who had also worked in a state mental hospital in New York, wrote:

“Asylums offer a life of its own special protection and limitations...for some patients to live through their psychoses and merge from their depths as saner and more stable people...It was not wholesale closure that the state hospitals needed, but fixing: dealing with the overcrowding, the understaffing, the negligence and brutalities... We forgot the benign aspects of asylums, or perhaps we felt that we could no longer afford to pay for them: the spaciousness and sense of community, the place for work and play, and for the gradual learning of social and vocational skills—a safe haven.”

While it is doubtlessly better if patients are enabled to be reintegrated with the community through housing in psychiatric care facilities and sheltered homes in the community, the important, traditional function of the IMH as an asylum should not be overlooked. We speak proudly of the inroads we made in the early detection of mental illness, we showcase innovations in mental health care, we highlight our success in restoring patients to their families, but we are shyly reticent of our role as an asylum—perhaps because that word by now has that derogatory connotation.

But the IMH should be proud too of its willingness to look after these patients and to provide—through all these decades—both a refuge for those who are unable to look after themselves and have no one else who can do that, and a sanctuary where they are sheltered, protected and cared for in a humane way.

REFERENCES

1. Ng BY. How the Mental Hospital was renamed Woodbridge Hospital in 1951. *Ann Acad Med Singapore* 1999;28:610-2.
 2. Shorter E. *A History of Psychiatry*. 1st ed. New York: John Wiley & Sons, Inc, 1997.
 3. Bachrach LL. Deinstitutionalization: promises, problems, and prospects, in *Mental Health Service Evaluation*. In: Knudsen HC, Thornicroft G, editors. Cambridge: Cambridge University Press, 1996.
 4. Bachrach LL. Deinstitutionalization: An Analytical Review and Sociological Perspective. Rockville: National Institute of Mental Health, 1976.
 5. Bachrach LL. A conceptual approach to deinstitutionalization. *Hosp Community Psychiatry* 1978;29:573-8.
 6. Thornicroft G, Bebbington P. Deinstitutionalisation: from hospital closure to service development. *Br J Psychiatry* 1989;155:739-53.
 7. Lamb HR. Lessons learned from deinstitutionalization in the US. *Br J Psychiatry* 1993;162:587-92.
 8. Teplin LA. The criminalization of the mentally ill: speculation in search of data. *Psychol Bull* 1983;94:54-67.
 9. Sacks O. The Lost Virtues of the Asylum. In: *The New York Review of Books*. New York: The New York Review of Books. Available at: <http://www.nybooks.com/articles/archives/2009/sep/24/the-lost-virtues-of-the-asylum/>. Accessed 26 June 2014.
-

Assessment of the American Joint Committee on Cancer 7th Edition Staging for Localised Prostate Cancer in Asia Treated with External Beam Radiotherapy

Meihua Wong,¹MBBS, Connie Yip,²MBChB, MRCP, FRCR, Huihua Li,³MS, PhD, Terence Tan,²FRCR, Ravindran Kanesvaran,¹MD, MRCP(UK), FAMS, Balram Chowbay,^{4,5,6}PhD, Puay Hoon Tan,⁷MBBS, FRCPA, MD, Min-Han Tan,^{1,8}MBBS, MRCP, PhD, Fuh Yong Wong,²MBBS, FRCR

Abstract

Introduction: Most international clinical practice guidelines for prostate cancer (PCa) are driven by data derived in a Western setting. However, tumour biology and clinical disease progression are likely to differ in the Asian population. We compare the performance of the revised American Joint Committee on Cancer (AJCC) prognostic groups with the commonly used D'Amico Risk Classification and conventional predictors for PCa, in a large cohort of Asian patients. **Materials and Methods:** We retrospectively reviewed data for 404 consecutive Singaporean patients receiving definitive radiotherapy at our centre between December 1996 and October 2006. The primary outcome was biochemical relapse-free survival (BRFS), defined using the Phoenix definition. The secondary outcome was overall survival (OS). Prognostic risk groups were defined using AJCC 7th edition (AJCC7) and 6th edition (AJCC6). Univariate analysis (UVA) and multivariate analysis (MVA) were performed for the following putative risk factors: age, Gleason score, prognostic grouping, tumour classification, radiation delivery technique, radiotherapy dose, hormonal therapy and initial PSA value. **Results:** For the cohort, median age was 69 years. Median follow-up was 66.3 months. Five-year BRFS rate was 84.3% with 71 biochemical relapses and 5-year OS rate was 89.1% with 54 deaths. The concordance-indices for BRFS prediction were 0.588, 0.550 and 0.567 for AJCC7, AJCC6 and D'Amico respectively. Initial PSA, T-stage and AJCC7 were prognostic for BRFS on UVA. Comparison of AJCC7 vs. D'Amico showed no statistical additional value of either classification system although D'Amico was superior when compared to AJCC6 in predicting BRFS. T-stage ≥ 3 and D'Amico were significant prognostic factors for BRFS on MVA. **Conclusion:** In our local, predominantly Chinese population, neither AJCC6 nor AJCC7 demonstrated a high predictive accuracy for BRFS although AJCC7 has a slightly better predictive ability than AJCC6.

Ann Acad Med Singapore 2014;43:484-91

Key words: D'amico, Intensity modulated radiotherapy, Prognosis, Risk stratification

¹Department of Medical Oncology, National Cancer Centre Singapore, Singapore

²Department of Radiation Oncology, National Cancer Centre Singapore, Singapore

³Health Services Research, Singapore General Hospital, Singapore

⁴Laboratory of Clinical Pharmacology, Division of Medical Sciences, Humphrey Oei Institute of Cancer Research, National Cancer Centre Singapore, Singapore

⁵Singhealth Clinical Pharmacology Core, Discovery Tower, Academia, Singapore

⁶Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

⁷Department of Pathology, Singapore General Hospital, Singapore

⁸Institute of Bioengineering and Nanotechnology, Singapore

Address for Correspondence: Dr Wong Fuh Yong, Department of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.

Email: ntrwfy@nccs.com.sg

Assessment of the American Joint Committee on Cancer 7th Edition Staging for Localised Prostate Cancer in Asia Treated with External Beam Radiotherapy

Meihua Wong,¹MBBS, Connie Yip,²MBChB, MRCP, FRCR, Huihua Li,³MS, PhD, Terence Tan,²FRCR, Ravindran Kanesvaran,¹MD, MRCP(UK), FAMS, Balram Chowbay,^{4,5,6}PhD, Puay Hoon Tan,⁷MBBS, FRCPA, MD, Min-Han Tan,^{1,8}MBBS, MRCP, PhD, Fuh Yong Wong,²MBBS, FRCR

Abstract

Introduction: Most international clinical practice guidelines for prostate cancer (PCa) are driven by data derived in a Western setting. However, tumour biology and clinical disease progression are likely to differ in the Asian population. We compare the performance of the revised American Joint Committee on Cancer (AJCC) prognostic groups with the commonly used D'Amico Risk Classification and conventional predictors for PCa, in a large cohort of Asian patients. **Materials and Methods:** We retrospectively reviewed data for 404 consecutive Singaporean patients receiving definitive radiotherapy at our centre between December 1996 and October 2006. The primary outcome was biochemical relapse-free survival (BRFS), defined using the Phoenix definition. The secondary outcome was overall survival (OS). Prognostic risk groups were defined using AJCC 7th edition (AJCC7) and 6th edition (AJCC6). Univariate analysis (UVA) and multivariate analysis (MVA) were performed for the following putative risk factors: age, Gleason score, prognostic grouping, tumour classification, radiation delivery technique, radiotherapy dose, hormonal therapy and initial PSA value. **Results:** For the cohort, median age was 69 years. Median follow-up was 66.3 months. Five-year BRFS rate was 84.3% with 71 biochemical relapses and 5-year OS rate was 89.1% with 54 deaths. The concordance-indices for BRFS prediction were 0.588, 0.550 and 0.567 for AJCC7, AJCC6 and D'Amico respectively. Initial PSA, T-stage and AJCC7 were prognostic for BRFS on UVA. Comparison of AJCC7 vs. D'Amico showed no statistical additional value of either classification system although D'Amico was superior when compared to AJCC6 in predicting BRFS. T-stage ≥ 3 and D'Amico were significant prognostic factors for BRFS on MVA. **Conclusion:** In our local, predominantly Chinese population, neither AJCC6 nor AJCC7 demonstrated a high predictive accuracy for BRFS although AJCC7 has a slightly better predictive ability than AJCC6.

Ann Acad Med Singapore 2014;43:484-91

Key words: D'amico, Intensity modulated radiotherapy, Prognosis, Risk stratification

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men, with a worldwide incidence of approximately 900,000 in 2008.¹ Internationally, there is marked variation in incidence, ranging from 104.2 per 100,000 in some Western populations, to 4.1 per 100,000 in South and Central Asia.¹ However, there has recently been a reported increase in incidence and mortality from PCa in various Asian countries.² In Singapore, the age-standardised incidence rates (ASIR) have risen from 8.3 per 100,000

(1983 to 1987) to 23.9 per 100,000 (2003 to 2007) in just 20 years. The ASIR in Singapore has reached 28.7 per 100,000, more than double that in Shanghai, China (ASIR of 11.3 per 100,000) or Mumbai, India (ASIR of 11.5 per 100,000).³ This may be attributed in part to increased PSA screening, the availability of transrectal ultrasound and extended sextant biopsies for prostate cancer detection in the late 1990s, although there may be other still unknown contributing factors.⁴

¹Department of Medical Oncology, National Cancer Centre Singapore, Singapore

²Department of Radiation Oncology, National Cancer Centre Singapore, Singapore

³Health Services Research, Singapore General Hospital, Singapore

⁴Laboratory of Clinical Pharmacology, Division of Medical Sciences, Humphrey Oei Institute of Cancer Research, National Cancer Centre Singapore, Singapore

⁵Singhealth Clinical Pharmacology Core, Discovery Tower, Academia, Singapore

⁶Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

⁷Department of Pathology, Singapore General Hospital, Singapore

⁸Institute of Bioengineering and Nanotechnology, Singapore

Address for Correspondence: Dr Wong Fuh Yong, Department of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.

Email: ntrwfy@nccs.com.sg

The majority of international clinical practice guidelines are largely driven by data derived in a Western setting. However, tumour biology and clinical disease progression may differ in the Asian population. Polymorphic variants in the region of 8q24 and 17q have been found to have a cumulative and significant association in prostate cancer.⁵ There are differences in prostate cancer risk-allele frequencies in an Asian population from Singapore compared to the Caucasian and African cohorts, although the biological significance of these genetic variants has yet to be fully elucidated.⁶ A study of prostate cancer incidence and survival in immigrants to Sweden found that the group of non-European immigrants of mainly Middle East, Asian, North African, and Chilean origin had the most favourable survival in the disease, and the calculated hazard ratio of mortality was 0.60 (range, 0.45 to 0.81).⁷ It has yet to be determined conclusively that the adoption of these guidelines in the Asian clinical practice is appropriate, as there is limited data on long-term outcomes of definitive radiotherapy in Asia. The absence of such reported outcomes is of concern given the increasing incidence of prostate cancer in Asia.²

Additionally, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual has recently been revised to its 7th edition. The new prognostic grouping for prostate cancer integrates both prostate specific antigen (PSA) and Gleason score (GS). Limited information on the extent of stage reclassification and the impact of this new approach on the estimation of clinical outcomes such as BRFS in a clinical setting is available. We thus seek to validate the performance of the revised AJCC groups, in comparison to the previous 6th edition and the commonly used D'Amico Risk Classification, in a large and uniform cohort receiving definitive radiotherapy with or without androgen-deprivation therapy in an Asian tertiary cancer centre. We also evaluated the performance of classical PCa prognostic factors derived from Western settings in this population, which is particularly salient given the paucity of such information in Asia.

Materials and Methods

Institutional Review Board approval was obtained for this retrospective study.

Clinical data were collected for 404 consecutive Singaporean patients with localised adenocarcinoma of the prostate (clinical stage T1-T4, NX/N0/N1, M0) who underwent definitive radiotherapy between December 1996 and October 2006 at the National Cancer Centre Singapore. Patients' characteristics are listed in Table 1.

Treatment

All patients received definitive radiotherapy up to a median total dose of 70 Gy (range, 66 to 80 Gy). Neoadjuvant

Table 1. Patient Characteristics

Characteristics				Number (%) n = 404
Age				
Median (range)				69 years (47 to 86)
Race				
Chinese				347 (85.9%)
Malay				23 (5.7%)
Indians				26 (6.4%)
Others				8 (2.0%)
Clinical classification stage				
T1				194 (48.0%)
T2				139 (34.4%)
T3				61 (15.1%)
T4				6 (1.5%)
No data available				4 (1.0%)
Initial PSA (ng/mL)				
<10.0				126 (31.2%)
10 to 20.0				102 (25.2%)
>20				170 (42.1%)
No data available				6 (1.5%)
Gleason score				
≤6				129 (39.1%)
7				173 (42.8%)
8 to 10				57 (14.1%)
No data available				16 (4.0)
Prognostic groups (AJCC, 7th edition)				
Group I	TNM	PSA	Gleason	62 (15.3%)
	T1a-c N0 M0	<10	≤6	
	T2a N0 M0	<10	≤6	
	T1-2a N0 M0	X	X	
Group IIA	TNM	PSA	Gleason	121 (30.0%)
	T1a-c N0 M0	<20	7	
	T1a-c N0 M0	≥10<20	≤6	
	T2a N0 M0	≥10<20	≤6	
	T2a N0 M0	<20	7	
	T2b N0 M0	<20	≤7	
	T2b N0 M0	X	X	
Group IIB	TNM	PSA	Gleason	151 (37.4%)
	T2c N0 M0	Any	Any	
	T1-2 N0 M0	≥20	Any	
	T1-2 N0 M0	Any	≥8	
Group III	TNM	PSA	Gleason	60 (14.9%)
	T3a-b N0 M0	Any	Any	

AJCC: American Joint Committee on Cancer

TNM: Tumour, Node, Metastasis

PSA: Prostate-specific antigen

Table 1. Patient Characteristics (Con't)

Characteristics				Number (%) n = 404
Prognostic groups (AJCC, 7 th edition)				
Group IV	TNM	PSA	Gleason	9 (2.2%)
	T4 N0 M0	Any	Any	
	Any T N1 M0	≥20	Any	
	Any T Any N M1	Any	Any	
Unclassifiable *even if PSA is not available, grouping can still be determined by T stage and/or either PSA or Gleason as available				1 (0.2%)
Prognostic groups (AJCC, 6 th edition)				
Group I	TNM	Grade		0 (0%)
	T1a N0 M0	1		
Group II	TNM	Grade		331 (81.9%)
	T1a N0 M0	2 – 4		
	T1b N0 M0	Any		
	T1c N0 M0	Any		
	T1 N0 M0	Any		
	T2 N0 M0	Any		
Group III	TNM	Grade		60 (14.9%)
	T3 N0 M0	Any		
Group IV	TNM	Grade		9 (2.2%)
	T4 N0 M0	Any		
	Any T N1 M0	Any		
	Any T Any N M1	Any		
Unclassifiable				4 (1.0%)
D’Amico				
Low risk				61 (15.1%)
Intermediate risk				119 (29.5%)
High risk				221 (54.7%)
Unclassifiable				3 (0.7%)

AJCC: American Joint Committee on Cancer

TNM: Tumour, Node, Metastasis

PSA: Prostate-specific antigen

hormonal therapy was given to 85 patients (21.0%) for a median duration of 2 months (range, 0.5 to 11.5 months). Treatment characteristics are reported in Table 2.

Patient Evaluation and Staging

All patients underwent a history and physical examination, initial serum PSA measurement and histologic confirmation of prostate adenocarcinoma. Tumour staging was performed according to the 6th and 7th edition of the AJCC Cancer Staging Manual (AJCC6 and AJCC7 respectively). In addition, patients were also classified according to the D'Amico Risk Classification.⁸

Table 2. Treatment Characteristics

Treatment	Number (%)
Hormonal therapy	
Neoadjuvant	
Only	17 (19.1%)
+ concurrent HT	14 (15.7%)
+ concurrent HT + adjuvant HT	54 (60.7%)
Concurrent + adjuvant HT	1 (1.1%)
Adjuvant only	3 (3.4%)
RT dose (Gy)	
60 ≤ RT dose < 70	27 (6.7%)
≥ 70	377 (93.3%)
RT technique	
IMRT	57 (14.1%)
Conformal	257 (63.6%)
No data available	90 (22.3%)

HT: Hormonal therapy; RT: Radiation therapy; IMRT: Intensity modulated radiation therapy

Statistical Analysis

The primary outcome was BRFS, defined as the time from the end of radiotherapy to the date of biochemical relapse as per the 2005 Phoenix definition.⁹ Patients were censored at the date of last clinical follow-up or death. Overall survival (OS), the secondary outcome, was defined from the diagnosis date to death date, or last follow-up date for censored cases. Both BRFS and OS were estimated by the Kaplan-Meier method. Univariate analysis (UVA) was performed for known prognostic factors: age, AJCC prognostic risk groupings, tumour classification, Gleason score, radiation delivery technique, radiation therapy (RT) dose, hormonal therapy, and PSA value at the time of first positive biopsy. Multivariate analysis (MVA) was performed by means of reduced model selection by including those prognostic factors with $P < 0.2$ on UVA. Proportional hazards assumptions were verified systematically for all proposed models.

Likelihood ratio test of nested models were performed to compare AJCC7/AJCC6 to D'Amico. Harrell's c-index was calculated to evaluate the concordance between predicted and observed responses of individual subjects separately. The c-index is commonly used to measure the performance of prediction models; $c = 1$ indicates the model has perfect predictive accuracy and $c = 0.5$ implies no predictive ability (random concordance). The proportion of the variation explained by each constituent component against the full predictive model is quantified by the Adequacy Index.¹⁰

All analyses were done using R 3.0.2 (Available at: <http://www.R-project.org>) and STATA 11 (STATA Corporation, College Station, TX USA), and all tests were 2-sided with a significance level of 0.05.

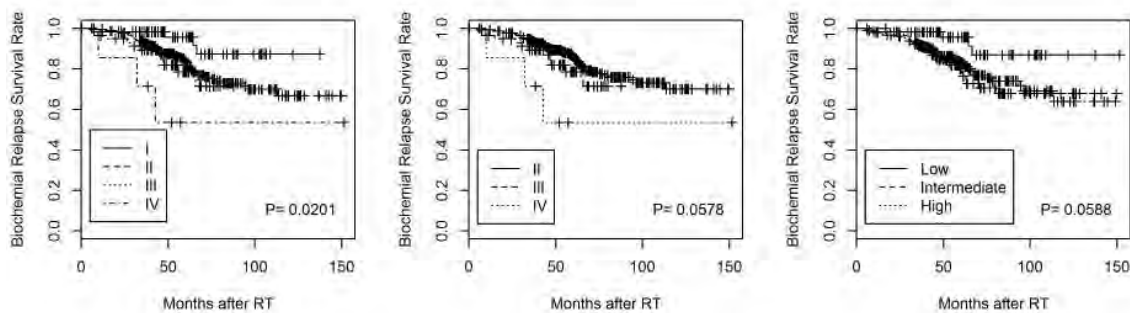


Fig. 1. Biochemical relapse free survival of patients in AJCC7, AJCC6 and D'Amico classification.

Results

Patient Characteristics

Median age for the entire cohort was 69 years (range, 47 to 86 years). Median PSA was 15.5 ng/mL (range, 1.0 to 290.0 ng/mL). See Table 1 for patient characteristics. Median follow-up was 66.3 months (range, 5.3 to 155.1 months). There were 71 biochemical relapses with 5-year BRFS of 84% (Fig. 1). Five-year overall survival rate was 89% with a total of 54 deaths in our study cohort. Eleven deaths (20.4%) were attributable to PCa.

AJCC Staging

There was a migration of stage II patients to stage I with AJCC7. The proportion of patients with stage II disease decreased from 81.9% to 67.4%, whilst patients with stage I disease increased from 0% to 15.3%. There were slightly more patients in the IIB subcategory (37.4%) than in the IIA subcategory (30.0%). There was no change to the proportion of patients with stage III and IV disease (14.9% and 2.2% respectively) (Table 1).

Predictive Accuracy

The results of the UVA and MVA for the various BRFS prognostic factors are summarised in Table 3. Initial PSA value ($P = 0.0147$), clinical T-stage ($P = 0.0026$), and AJCC7 ($P = 0.0201$) were significant prognostic factors on UVA. D'Amico intermediate/high risks group and T4 disease were the only significant prognostic factor following MVA (Table 3).

None of the risk stratification instruments prognosticated for BRFS well although AJCC7 performed marginally better compared to AJCC6 and D'Amico's in our cohort of patients, with c-indices of 0.588, 0.550 and 0.567 respectively (Fig. 1).

The results of likelihood ratio tests for AJCC7 and D'Amico against their nested models are shown in Table

4A. Neither AJCC7 nor D'Amico shows additional statistical value relative to each other for BRFS or OS; however, the addition of D'Amico to AJCC7 showed significant statistical improvement ($P = 0.0378$) for PCa specific survival (CSS). In contrast, D'Amico shows significantly better prognostic power for BRFS compared to AJCC6 (Adequacy index 96.9% vs. 59.3%, respectively, $P = 0.0169$) whereas AJCC6 shows better prognostic power for OS compared to D'Amico (Adequacy index 70.7% vs. 42.4%, respectively, $P = 0.0395$) (Table 4B). Taking their c-indices into consideration, these likelihood ratio tests suggested an additional contribution of AJCC7 over and above AJCC6 in prognosticating BRFS. AJCC6 cannot be compared directly to AJCC7 using likelihood ratio test because of their identical classification of stage III and IV patients.

In contrast to the poor predictive power of these staging instruments for BRFS, they were demonstrably better at prognosticating OS (Fig. 2). In UVA, both AJCC7 and AJCC6 were significant prognosticators of OS with c-indices of 0.612 and 0.570 respectively. Age ($P = 0.0072$) and T-stage ($P = 0.0158$) were also predictive of OS in UVA (Table 5). Notably, initial PSA value which was not useful in prognosticating OS ($P = 0.491$) was significantly prognostic for BRFS as well as being the sole prognosticator for CSS ($P = 0.0012$). In MVA, age, T-stage, hormonal therapy and D'Amico risk groups were predictive of OS (Table 5).

Discussion

Our study evaluated the clinical outcomes of patients with prostate cancer treated with definitive radiotherapy in a large tertiary cancer centre that serves approximately 70% of all cancer patients in this country. Patients were treated with standard departmental radiotherapy protocols with minimal protocol deviations.

In our local, predominantly Chinese population, neither

Table 3. Univariate and Multivariate Analysis of Prognostic Factors for BRFS

Prognostic factors	Univariate analysis	Multivariate analysis	
	P value	P value	HR (95% CI)
Initial PSA value (continuous variable)	0.0147	Not significant on MVA	
Prognostic risk groups (AJCC, 7 th edition)	0.0201		
Prognostic risk groups (AJCC, 6 th edition)	0.0578		
Prognostic risk groups (D'Amico)	0.0588	Reference	
Low risk			
Intermediate risk			
High risk		0.0449	2.99 (1.03, 8.71)
T-stage (continuous variable)	0.0026	0.1930	2.05 (0.70, 6.03)
T1		Reference	
T2			
T3			
T4		0.1437	1.50 (0.87, 2.60)
RT dose (60 to 70 Gy vs >70 Gy)	0.1057	0.0755	2.01 (0.93, 4.36)
HT (any vs none)	0.4129	0.0032	9.54 (2.13, 42.65)
Gleason score (≤ 6 vs ≥ 7 vs ≥ 8)	0.1403	Not significant on MVA	
Age (continuous variable)	0.2471		
RT delivery technique (IMRT vs non-IMRT)	0.4261		

BRFS: Biochemical relapse-free survival; PSA: Prostate-specific antigen; AJCC: American Joint Committee on Cancer; RT: Radiation therapy; HT: Hormonal therapy; IMRT: Intensity modulated radiation therapy; MVA: Multivariate analysis

Table 4A. Comparison of AJCC7 and D'Amico as Predicators of BRFS, OS and CSS

Full model	Likelihood		P value		Adequacy index	
	AJCC7	D'Amico	AJCC7*	D'Amico†	AJCC7‡	D'Amico§
BRFS						
12.36	10.03	7.12	0.1555	0.3125	81.1%	57.6%
OS						
11.65	10.06	5.57	0.1081	0.4523	86.4%	47.8%
CSS						
9.02	2.47	7.63	0.7076	0.0378	27.4%	84.6%

AJCC: American Joint Committee on Cancer; BRFS: Biochemical relapse-free survival; OS: Overall survival; CSS: PCa specific survival

*The comparison of the model with the predictor of D'Amico only with the one with predictors of both AJCC7 and D'Amico.

†The comparison of the model with the predictor of AJCC7 only with the one with predictors of both AJCC7 and D'Amico.

‡The proportion of the variation explained by AJCC7 compared to that explained by both AJCC7 and D'Amico.

§The proportion of the variation explained by D'Amico compared to that explained by both AJCC7 and D'Amico.

Table 4B. Comparison of AJCC6 and D'Amico as Predicators of BRFS, OS and CSS

Full model	Likelihood		P value		Adequacy index	
	AJCC6	D'Amico	AJCC6*	D'Amico†	AJCC6‡	D'Amico§
BRFS						
12.38	4.22	6.90	0.0643	0.0169	34.1%	55.7%
OS						
11.21	7.93	4.75	0.0395	0.1942	70.7%	42.4%
CSS						
8.32	2.39	6.98	0.5115	0.0514	28.7%	83.9%

AJCC: American Joint Committee on Cancer; BRFS: Biochemical relapse-free survival; OS: Overall survival; CSS: PCa specific survival

*The comparison of the model with the predictor of D'Amico only with the one with predictors of both AJCC7 and D'Amico.

†The comparison of the model with the predictor of AJCC7 only with the one with predictors of both AJCC7 and D'Amico.

‡The proportion of the variation explained by AJCC7 compared to that explained by both AJCC7 and D'Amico.

§The proportion of the variation explained by D'Amico compared to that explained by both AJCC7 and D'Amico.

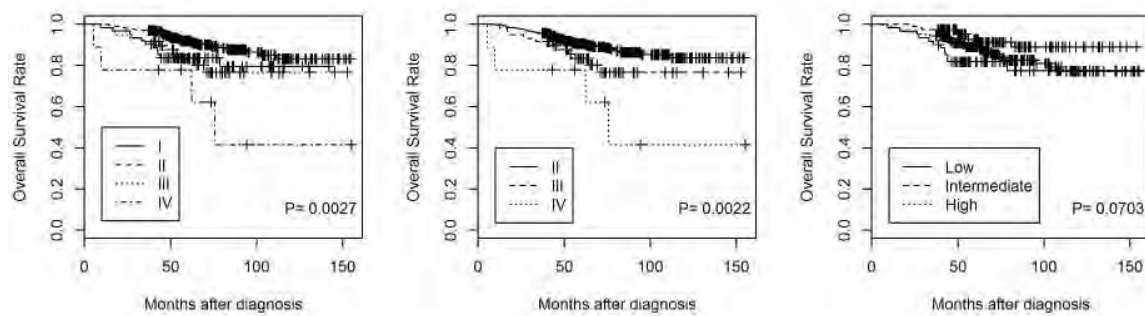


Fig. 2. Overall survival of patients in AJCC7, AJCC6 and D'Amico classification.

Table 5. Univariate and Multivariate Analysis of Prognostic Factors for OS

Prognostic factors	Univariate analysis	Multivariate analysis	
	P value	P value	HR (95% CI)
Age (continuous variable)	0.0072	0.0013	1.08 (1.03, 1.13)
Prognostic risk groups (AJCC, 7th edition)	0.0027	Not significant on MVA	
Prognostic risk groups (AJCC, 6th edition)	0.0022		
T-stage (continuous variable)	0.0158		
T1		Reference	
T2		0.0100	2.55 (1.25, 5.21)
T3		0.0020	4.36 (1.72, 11.06)
T4		<0.0001	29.77 (5.78, 153.36)
Prognostic risk groups (D'Amico)	0.0703	Reference	
Low Risk		Reference	
Intermediate Risk		0.0020	0.23 (0.09, 0.59)
High Risk		0.0072	0.32 (0.14, 0.74)
HT (any vs none)	0.0600	0.0167	0.31 (0.12, 0.81)
RT delivery technique (IMRT vs non-IMRT)	0.0483	Not significant on MVA	
Initial PSA value	0.4911		
RT dose (60 to 70 Gy vs. >70 Gy)	0.1201		
Gleason score (≤ 6 vs. 7 vs ≥ 8)	0.3542		

OS: Overall survival; AJCC: American Joint Committee on Cancer; HT: Hormonal therapy; RT: Radiation therapy; PSA: Prostate-specific antigen; MVA: Multivariate analysis

AJCC6 nor AJCC7 demonstrates a high predictive accuracy for BRFS although AJCC7 ($c = 0.588$) has a slightly better concordance with BRFS than AJCC6 ($c = 0.550$) or D'Amico ($c = 0.567$). Our results are consistent with the findings reported in a study by Zaorsky et al which compared the ability of AJCC6 and AJCC7 to predict biochemical failure as per the 2005 Phoenix definition, in 2469 men with locally advanced prostate who received definitive RT with or without adjuvant hormonal therapy.¹¹ In this study, the concordance probability estimate (CPE) for biochemical failure for AJCC6 was 0.51 ± 0.009 , and the CPE for AJCC7 was 0.59 ± 0.02 . The substratification of stage IIA and IIB was also not prognostic.

Interestingly, we noted that higher risks patients in the

D'Amico risk classification were more likely to sustain a biochemical failure but were significantly less likely to die overall. While this non-intuitive observation may be due to chance, the protective effects of additional adjuvant hormonal treatment for the high-risk patients or other confounders may be contributory. PCa patients at higher risks of relapse or who have relapsed often undergo extended periods of hormonal therapy. The incidence of hormonal therapy in the low, intermediate and high risks D'Amico group was 8.2%, 18.5% and 28.1% ($P = 0.0016$) respectively and use of hormonal therapy was independently predictive of improved survival ($P = 0.0167$, 95% CI, 0.12 to 0.81) on MVA.

The AJCC7 prognostic groups incorporate 3 well

acknowledged prognostic factors, PSA, Gleason score and T-stage. However, only initial PSA value, T-stage and AJCC7 were found to be significant predictors for BRFs in our local population on UVA; no significant association was found for Gleason score. There are several possibilities to explain our findings if there is indeed a true relationship between Gleason score and biochemical relapse. First, the true biological effect of poor tumour differentiation could be confounded by treatment bias as more patients with high Gleason scores could be treated with hormonal therapy that delayed biochemical failure. Besides that, not all of our pathological specimens were centrally reviewed and hence, inter-observer variability which could affect concurrence, consistency and reproducibility of Gleason score, as delineated in several studies, could be another potential confounding factor.^{12,13} Our study also spanned over a decade when progressive modifications in the Gleason scoring system have occurred.^{14,15} Overall, the subtle differences in grading could have biased the effect towards null. Finally, the major prognostic impact for tumour differentiation may be related to higher Gleason scores of 9 to 10, which were present in only a small proportion (7.4%) of our patients.

In contrast to our study, Gleason score has been validated as a significant predictor of BRFs, together with PSA and T-stage in a Japanese retrospective study with 679 patients.¹⁶ However, it is difficult to compare the 2 studies because different definitions of biochemical relapse are used. The 2005 Phoenix definition of PSA nadir plus 2 ng/mL for biochemical failure is used in this study instead of the 1996 ASTRO definition which was used in the Japanese study, because it has been assessed and found to have better concordance with clinical outcome in an Asian population.¹⁷ This would undoubtedly affect the interpretation of these results as PSA definition is integral to the identification of patients with biochemical relapse and could account for the difference in the 5-year BRFs between that reported in the Japanese study (71.9%) and ours (84%). For the same reason, it is difficult to compare our results to previous studies which validated Gleason score as a significant prognostic factor for BRFs using the ASTRO definition for biochemical relapse. Moreover, our study is not the first to report a negative finding for Gleason score as a predictor for biochemical failure. Pellizzon et al¹⁸ evaluated several prognostic factors for biochemical failure in 209 patients with locally advanced prostate cancer treated with external beam radiotherapy and high dose rate brachytherapy. The authors found that Gleason score was a significant prognostic factor on UVA but not on MVA.

Conclusion

In conclusion, the AJCC7 prognostic grouping performed marginally better than AJCC6 or D'Amico Risk

Classification in prognosticating BRFs. Additionally, our findings suggest that clinical T-stage is the most significant prognostic factor for disease control and survival in our population and the commonly used D'Amico Risk Classification continued to be of relevance in prognosticating outcomes and guide treatment of the Asian prostate cancer patient.

Acknowledgments

This paper was submitted in abstract form to the American Society of Clinical Oncology Genitourinary Cancers Symposium in 2011. We thank Hou Xuan from Clinical Trials Epidemiological Sciences, National Cancer Centre Singapore, for assistance in analysing the data. The National Cancer Centre Research Fund provided funding for this study.

REFERENCES

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. France: International Agency for Research on Cancer, 2010. Available at: <http://globocan.iarc.fr>. Accessed 8 March 2013.
2. Sim HG, Cheng CW. Changing demography of prostate cancer in Asia. *Eur J Cancer* 2005;41:834-45.
3. Chia SE, Tan CS, Lim GH, Sim X, Lau W, Chia KS. Incidence, mortality and five-year relative survival ratio of prostate cancer among Chinese residents in Singapore from 1968 to 2002 by metastatic staging. *Ann Acad Med Singapore* 2010;39:466-71.
4. Chia SE, Tan CS, Lim GH, Sim X, Pawitan Y, Reilly M, et al. Incidence, mortality and survival patterns of prostate cancer among residents in Singapore from 1968 to 2002. *BMC Cancer* 2008;8:368.
5. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, et al. Cumulative association of five genetic variants with prostate cancer. *New Engl J Med* 2008;358:910-9.
6. Chan JY, Li H, Singh O, Mahajan A, Ramasamy S, Subramanian K, et al. 8q24 and 17q prostate cancer susceptibility loci in a multiethnic Asian cohort. *Urol Oncol* 2013;31:1553-60.
7. Hemminki K, Ankerst DP, Sundquist J, Mousavi SM. Prostate cancer incidence and survival in immigrants to Sweden. *World J Urol* 2013;31:1483-8.
8. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-74.
9. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965-74.
10. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.
11. Zaorsky NG, Li T, Devarajan K, Horwitz EM, Buysyounouski MK. Assessment of the American Joint Committee on Cancer staging (sixth and seventh editions) for clinically localized prostate cancer treated with external beam radiotherapy and comparison with the National Comprehensive Cancer Network risk-stratification method. *Cancer* 2012 15;118:5535-43.

12. Burchardt M, Engers R, Muller M, Burchardt T, Willers R, Epstein J. Interobserver reproducibility of Gleason grading: evaluation using prostate cancer tissue microarrays. *J Cancer Res Clin Oncol* 2008;134:1071-8.
 13. Brimo F, Schultz L, Epstein JI. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. *J Urol* 2010;184:126-30.
 14. Billis A, Guimaraes MS, Freitas LL, Meirelles L, Magna LA, Ferreira U. The impact of the 2005 international society of urological pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. *J Urol* 2008;180:548-52.
 15. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2005;29:1228-42.
 16. Nakamura K, Mizowaki T, Imada H, Karasawa K, Uno T, Onishi H, et al. External-beam radiotherapy for localized or locally advanced prostate cancer in Japan: a multi-institutional outcome analysis. *Jpn J Clin Oncol* 2008;38:200-4.
 17. Ramalingam M, Lau W, Tan T, Fook S, Ngoi F, Cheng C. Asians with localized prostate cancer treated with 3-dimensional conformal radiation therapy and adjuvant hormonal therapy: comparing Phoenix and American Society of Therapeutic Radiology and Oncology (ASTRO) definitions in an Asian population. *Urology* 2008;71:506-10.
 18. Pellizzon AC, Salvajoli J, Novaes P, Maia M, Fogaroli R, Gides D, et al. The relationship between the biochemical control outcomes and the quality of planning of high-dose rate brachytherapy as a boost to external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. *Int J Med Sci* 2008;5:113-20.
-

Changes in Mechanical, Structural Integrity and Microbiological Properties Following Cryopreservation of Human Cadaveric Iliac Arteries

Stephen KY Chang, ¹*MBBS (S'pore), MMed(Surg)(S'pore), FRCSEd(Gen Surg)*, Joel WL Lau, ¹*MBBS*, Chee Kong Chui, ¹*Phd*

Abstract

Introduction: The study seeks to investigate how the duration of storage of cryopreserved human cadaveric iliac arteries impacts their mechanical, structural and microbiological properties as compared to their fresh sample. **Materials and Methods:** Iliac arteries were harvested from 12 human cadavers and divided into 2 groups. One group underwent mechanical stress-strain assessment immediately and another was cryopreserved for a pre-determined time-period (range, 29 to 364 days). Mechanical functionality was assessed with a customised clamping mechanism. The arteries' microbiological properties were studied pre- and post-cryopreservation. The post-thawed arteries were also assessed histologically for structural integrity. **Results:** Of the 12 pairs, only 7 (58, 119, 150, 252, 300, 332 and 364 days) iliac arteries were included in the final analysis. The other 5 pairs (29, 90, 188, 205 and 270 days) had abundant local calcification and their stress-strain curves could not be characterised. From the curves, pre- and post-cryopreserved arteries had the most similar mechanical properties when stored for 119 days. A trend of increasing relative stiffness with increased duration of storage was noted. The post-thawed arteries demonstrated minimal fragmentation except in atherosclerotic areas. Majority of the arteries were not contaminated by bacterial or fungal infection pre- and post-cryopreservation. Also, 2 arteries (364 and 332 days) which had initial bacterial colonisation showed no bacterial growth on their post-thawed sample. **Conclusion:** Mechanically, non-atherosclerotic cryopreserved arteries can be a good substitute to their corresponding fresh arterial graft. However, the length of cryopreservation has an effect on the relative stiffness of the pre- and post-cryopreserved arteries. Histological and microbiological findings suggest that cryopreservation have little impact on an artery structural integrity and may possibly have a role in maintaining sterility and sterilising the arteries.

Ann Acad Med Singapore 2014;43:492-8

Key words: Arterial allograft, Human arteries, Stress-strain curves, Vascular cryopreservation

¹Department of Surgery, National University Hospital, Singapore

Address for Correspondence: A/Prof Stephen KY Chang, Department of Surgery, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: cfscky@nus.edu.sg

Changes in Mechanical, Structural Integrity and Microbiological Properties Following Cryopreservation of Human Cadaveric Iliac Arteries

Stephen KY Chang, ¹MBBS (S'pore), MMed(Surg)(S'pore), FRCSEd(Gen Surg), Joel WL Lau, ¹MBBS, Chee Kong Chui, ¹Phd

Abstract

Introduction: The study seeks to investigate how the duration of storage of cryopreserved human cadaveric iliac arteries impacts their mechanical, structural and microbiological properties as compared to their fresh sample. **Materials and Methods:** Iliac arteries were harvested from 12 human cadavers and divided into 2 groups. One group underwent mechanical stress-strain assessment immediately and another was cryopreserved for a pre-determined time-period (range, 29 to 364 days). Mechanical functionality was assessed with a customised clamping mechanism. The arteries' microbiological properties were studied pre- and post-cryopreservation. The post-thawed arteries were also assessed histologically for structural integrity. **Results:** Of the 12 pairs, only 7 (58, 119, 150, 252, 300, 332 and 364 days) iliac arteries were included in the final analysis. The other 5 pairs (29, 90, 188, 205 and 270 days) had abundant local calcification and their stress-strain curves could not be characterised. From the curves, pre- and post-cryopreserved arteries had the most similar mechanical properties when stored for 119 days. A trend of increasing relative stiffness with increased duration of storage was noted. The post-thawed arteries demonstrated minimal fragmentation except in atherosclerotic areas. Majority of the arteries were not contaminated by bacterial or fungal infection pre- and post-cryopreservation. Also, 2 arteries (364 and 332 days) which had initial bacterial colonisation showed no bacterial growth on their post-thawed sample. **Conclusion:** Mechanically, non-atherosclerotic cryopreserved arteries can be a good substitute to their corresponding fresh arterial graft. However, the length of cryopreservation has an effect on the relative stiffness of the pre- and post-cryopreserved arteries. Histological and microbiological findings suggest that cryopreservation have little impact on an artery structural integrity and may possibly have a role in maintaining sterility and sterilising the arteries.

Ann Acad Med Singapore 2014;43:492-8

Key words: Arterial allograft, Human arteries, Stress-strain curves, Vascular cryopreservation

Introduction

Advancement in cryopreservation techniques have led to mounting interest in the use of arterial allograft for vascular reconstructive procedures and for treating arterial infections.^{1,2} Cryopreservation of arterial allografts at deep sub-zero temperature offers the benefit of ensuring a ready supply of vascular tissues for emergency use or when electively needed. At deep sub-zero temperature, all biochemical reactions that lead to cell death are effectively stopped. Theoretically, cryopreservation would thus offer indefinite longevity to cells and possibly indefinite storage.

Current cryopreservation techniques involve the use of cryoprotectants agents (CPA) and an automated gradual freezing and rewarming process to minimise cryoinjuries

and improve tissue preservation.³⁻⁵ However, the effects of storage time on vascular allograft have yet to be extensively studied.

The long-term safety of the use of cryopreserved arterial grafts is influenced by its post-thawed haemodynamic properties, arterial tone and susceptibility to infections.^{2,6,7} These factors can be measured via changes in mechanical properties, extent of disruption of the arterial structural integrity and microbiology results of the pre- and post-cryopreserved arteries. Deficiencies in these aspects can lead to the development of secondary vascular disease and eventual failure of vascular grafts.^{8,9}

The aim of this study is to analyse and evaluate the effects

¹Department of Surgery, National University Hospital, Singapore

Address for Correspondence: A/Prof Stephen KY Chang, Department of Surgery, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: cfscky@nus.edu.sg

of variable storage time on (i) the mechanical properties, (ii) structural integrity, and (iii) microbiological properties of pre- and post-cryopreserved human cadaveric iliac arteries.

Materials and Methods

Iliac arteries were harvested from 12 human cadavers aged between 45 and 71 years. Two iliac arteries were obtained from each cadaver, where they were excised from the end of the abdominal aorta. Arteries were removed immediately after death and transported to the laboratory in an ice box with histidine-tryptophan-ketoglutarate (HTK) solution before the experiments. The arteries were kept in HTK solution prior to cryopreservation or mechanical stress-strain testing for not more than 1 hour at room temperature. HTK solution is used to preserve the arteries during its hypothermic transport to the laboratory.

The iliac arteries from each donor were divided into 2 groups (Group A and Group B) and each artery was cut further into 2 pieces, one measuring 40 mm and the other measuring 10 mm. The 40 mm artery was used for mechanical stress-strain assessment while the 10 mm piece was used for pre-microbiological properties assessment. Group A underwent mechanical stress-strain assessment within 1 hour of its arrival to the laboratory as well as microbiology evaluation within 24 hours from harvesting. Group B underwent cryopreservation via a standardised protocol and each artery had its mechanical, histological and microbiological properties assessed only after a pre-determined period of time between 29 days and 364 days.

The arteries in Group B were preserved in 10% dimethylsulphoxide (DMSO). The DMSO was added gradually in 4 x 5 minutes steps (2.5%, 5%, 7.5% and 10% dilution of DMSO). The arteries were then subjected to automated controlled freezing in a biological freezer at a temperature reduction rate of 1°C/min. The frozen iliac artery segment was stored in liquid nitrogen at -150°C for a pre-determined period of time ranging from 29 days to 364 days.

After a pre-determined storage period, the iliac artery segment underwent a staged thawing process. The artery was transferred from the storage tank and thawed at 37°C water bath within 20 minutes. Following which, the arteries were allowed to equilibrate with 5% DMSO at room temperature for 20 minutes. The cryoprotectant additives were removed gradually via dilution in a Dulbecco's Modified Eagle Medium (DMEM) at room temperature for 20 minutes.

A mechanical property testing apparatus was designed and built to access the mechanical properties of vascular tissues.¹⁰ A customised clamping mechanism was also designed to ensure a uniformly distributed clamping force over the clamping area. In addition, a combined logarithm

and polynomial strain energy equation were applied to model the elastic response of the arteries.

Tao Yang et al¹⁰ described the apparatus as one which included a stepper motor (CTP21 DANAHER) employed to carry out basic motion such as elongation and a laser sensor (optoNCDT 1401-200, Micro-epsilon) equipped to control positioning. Also, load cells (LCM UF series) were employed to measure force imposed on the arteries and a circulator (Polyscience 8106) was employed to circulate the testing medium (Krebs Ringer solution) in the testing environment.

The stress-strain test was conducted in a water bath of circulating Krebs-Ringer solution with pH maintained at 7.3 to 7.4 and temperature at 37°C. This was done so that the experiments could be carried out in an environment that mimics body condition. Prior to testing, all visible connective tissues on the arteries were removed and all arteries had their stress-strain curve preconditioned to a steady state before data were collected. This is used to reduce variability in mechanical measurements.⁷ In our experiment, each artery underwent uniaxial elongation, longitudinally with a ramping speed controlled at 2.5 mm/second.

The changes in mechanical properties (before and after cryopreservation) were studied quantitatively by matching the stress and strain curves of a cryopreserved artery and its corresponding fresh controls. Pre- and post-cryopreserved arteries that had similar trends of within 20% match when elongated at 30% strain or more were considered a good match.¹¹

The arterial structural integrity was analysed via histological assessment. Samples of the artery were inked with both haematoxylin and eosin (H&E) stain and Elastic Van Gieson (EVG) to assess the extent of disruption of the internal and external elastic lamina layer after cryopreservation. The pre- and post-cryopreserved cadaveric arterial grafts were also evaluated for fungal growth and aerobic and anaerobic bacterial colonisation.

Results

Cryopreservation had been performed for a total of 12 pairs of human cadaveric arteries. The duration of storage of the cryopreserved iliac arteries ranged from 29 days to 364 days. The mechanical, histological and microbiological properties were evaluated (Tables 1 and 2).

The stress-strain curves of the cryopreserved and fresh controls of the same artery were matched and the relationship of the curves was analysed (Fig. 1). Of the 12 pairs, 7 pre- and post-cryopreserved iliac arteries (58, 119, 150, 252, 300, 332 and 364 days) were evaluated. Out of the 7 specimens, all of them showed no evidence that cryopreservation will “weaken” an artery. Also, 4 post-thawed cryopreserved

Table 1. Histological Analysis of the Structural Integrity of Post-thawed Cryopreserved Arteries

Duration of storage	Histological properties		
	Atherosclerosis (AS)	Lumina elastica interna	Lumina elastica externa
364 days	Atherosclerosis (2/3)	Mild fragmentation (1/3) Areas involved by AS extensive fragmentation (3/3)	Mild fragmentation (1/3) Areas involved by AS not optimally visualised
332 days	No atherosclerosis	No fragmentation	No fragmentation
300 days	Atherosclerosis (1 – 2/3)	Moderate fragmentation (1 – 2/3) especially when AS is more pronounced	Moderate fragmentation (2/3) especially when AS is more pronounced
270 days	No atherosclerosis	No fragmentation	No fragmentation
252 days	Atherosclerosis (1/3)	Mild fragmentation (1/3)	Mild fragmentation (1/3)
205 days	Atherosclerosis (2 – 3/3)	Extensive fragmentation (2 – 3/3)	Mild fragmentation (1/3)
188 days	Atherosclerosis (1/3)	Mild fragmentation (1 – 3)	Mild fragmentation (1/3)
150 days	Atherosclerosis (1/3)	Mild fragmentation (1/3)	Mild fragmentation (1/3)
119 days	Atherosclerosis (2/3)	Mild fragmentation (1/3) Areas involved by AS extensive fragmentation (3/3)	Mild fragmentation (1/3) Areas involved by AS extensive fragmentation (3/3)
90 days		Not assessed due to incomplete section	
58 days	No atherosclerosis	Mild fragmentation (1/3)	Mild fragmentation (1/3)
29 days	No atherosclerosis	Mild fragmentation (1/3)	Mild fragmentation (1/3)

Table 2. Comparison of Microbiological Properties of Pre- and Post-Cryopreserved Arteries

Duration of storage	Bacterial culture*	Pre-cryopreserved microbiological properties†	Post-thawed microbiological properties†
364 days	Aerobic Anaerobic	<i>Acinetobacter</i> species <i>Delftia acidovorans</i> <i>Enterococcus faecalis</i>	Negative
332 days	Aerobic Anaerobic	Negative	Negative Negative
300 days	Aerobic Anaerobic	<i>Diphtheroid bacilli</i> Negative	Negative Negative
270 days	Aerobic Anaerobic	Negative Negative	Negative <i>Propionibacterium</i> species
252 days	Aerobic Anaerobic	Negative	Negative
205 days	Aerobic Anaerobic	Negative	Negative
188 days	Aerobic Anaerobic	Negative Negative	Negative
150 days	Aerobic Anaerobic	Negative Negative	Negative Negative
119 days	Aerobic Anaerobic	Negative Negative	Negative
90 days	Aerobic Anaerobic	Negative	Negative
58 days	Aerobic Anaerobic	Negative	Negative
29 days	Aerobic Anaerobic	Negative <i>Propionibacterium</i> species	Negative <i>Propionibacterium</i> species

*Bacterial growth was labelled as negative after 5 days of no bacterial growth.

†No fungal growth was detected after 14 days on pre- and post-thawed arteries for all duration of storage.

arteries showed good match with its fresh control on stress-strain curve within 30% strain. The match was noted to be good as mechanically, the stress-strain relationship of the arteries had a closeness of match of within 20% (arteries stored for 119, 150, 300 and 332 days). The remaining 5 pairs (29, 90, 188, 205 and 270 days) of arteries had abundant calcification noted on visual inspection. Their stress-strain curves were characterised by premature breaks and their elasticity were compromised due to stiffening of the arteries by calcification (Fig. 2).

From the experiments it was noted that the stress (i.e. pressure) required to strain (i.e. elongate) a cryopreserved artery as compared to its fresh artery varied with the duration of cryopreservation. At 58 days, the cryopreserved artery was noted to be less stiff as compared to its fresh sample. At 119 and 150 days of storage, the post-thawed arteries were noted to match the fresh samples tightly. This trend of increasing stiffness continued and at 364 days, the cryopreserved artery was noted to be much stiffer as compared to its corresponding fresh control (Fig. 1).

The histology of the 12 cryopreserved iliac arteries was analysed and most arteries showed minimal histological changes (Table 1). For the arteries noted to have atherosclerotic plaques present, fragmentation of the internal and external lumina elastica layers were noted. In addition, increased fragmentation was noted over the area involved by atherosclerosis (arteries stored for 119, 205, 300 and 364 days). Correspondingly, arteries with no or only mild atherosclerosis have no fragmentation or only mild fragmentation of the lumina elastica layers. All these arteries had well preserved cellularity of the medial layers. The luminal surface for all the arteries appeared to be well preserved with only some randomly distributed areas noted to be lacking endothelium.

For microbiological assessment, majority of both pre- and post-cryopreserved arteries did not have any bacterial (aerobic and anaerobic) or fungal growth after 5 and 14 days respectively (Table 2). Interestingly, for the artery stored for 300 and 364 days, its post-thawed bacterial culture failed to detect any bacterial growth though both aerobic and anaerobic species were detected initially before cryopreservation (Table 2). For the artery stored for 29 days, *Propionibacterium* species was grown in both pre- and post-cryopreservation. Only in 1 out of the 12 post-thawed artery, was bacterial cultured (*Propionibacterium* species) when previously no bacterial growth was noted in the pre-cryopreserved specimen (artery stored for 270 days).

Discussion

Cryopreservation is an important asset for the storage of arterial grafts. With an increasing interest in the

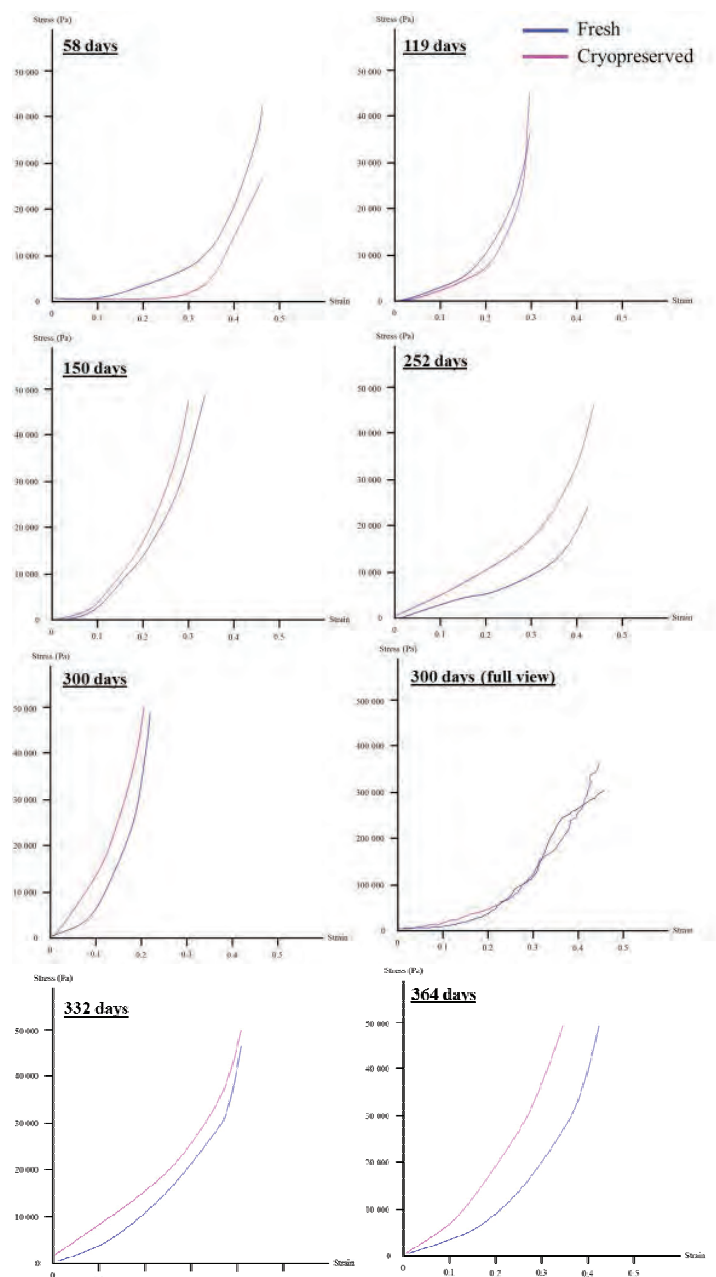


Fig. 1. Stress and strain curve of pre- and post-cryopreserved harvested human cadaveric iliac arteries (58, 119, 150, 252, 300, 332 and 364 days).

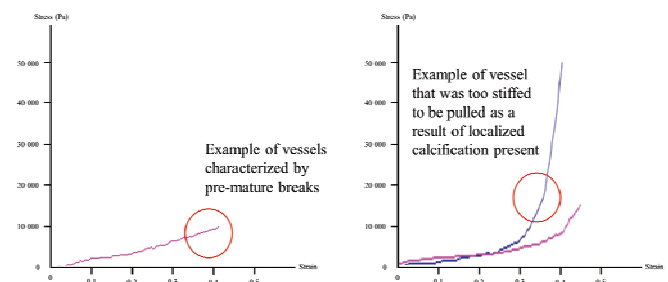


Fig. 2. Example of stress and strain curve of pre- and post-cryopreserved arteries with presence of abundant calcifications (for vessels stored for 29, 90, 188, 205 and 270 days).

establishment of vascular allograft tissue banks, assessing the long-term viability of arterial grafts has important implications. However, the effects of long-term storage have yet to be extensively studied. This experimental study is the first to compare the mechanical and microbiological properties of pre- and post-cryopreserved stored for up to 1 year.

Arterial allograft cryopreserved for short periods showed promising results in terms of excellence in haemodynamic graft patency, anticoagulant need and resistance to infection.^{12,13} From our study, uniaxial elongation of the arteries in a custom-designed apparatus¹⁰ helped determine the stress-strain mechanical properties of the arteries. The elasticity of the cryopreserved and fresh arteries matched (within 20%) with the arteries stretched at 1.3 times the original length (30% strain, 1.3 stretch ratio). This was so for 4 out of the 12 harvested iliac arteries. In addition, the experimental data for all 7 out of the 12 arteries showed no evidence that cryopreservation will “weaken” an artery (i.e. making it easier to break a low strain). As such, theoretically, cryopreserved and fresh iliac arteries are a suitable substitute for each other when based on their mechanical properties. This study parallels an observation made by Jorge et al¹⁴ who showed that mechanical properties of arteries were not significantly changed after cryopreservation for up to 2 months.

It was also observed that the duration of cryopreservation had an effect on the relative stiffness of the cryopreserved artery. In this study, the post-thawed cryopreserved artery was initially less stiff than its corresponding fresh control (58 days). This implies that less force was required to elongate the cryopreserved artery compared to its fresh control. We do not exactly understand the mechanism behind this finding; however, we postulate that it may be due to the variability of the arteries despite it being taken from the same donor. Then again, what was more apparent was that of a trend of increasing relative stiffness between pre- and post-cryopreserved arteries. The arteries appeared to be stiffer when the number of days of cryopreservation increased. After storage duration of 119 and 150 days, the stiffness of both pre- and post-cryopreserved arteries appears to match each other closely. Thereafter, the trend was that the cryopreserved arteries would require more force to elongate compared to its corresponding fresh arteries (252, 300, 332 and 364 days). This suggests that in the establishment of a vascular allograft tissue bank, vascular tissues cannot be stored indefinitely and perhaps arteries stored for up to 4 months would best mechanically substitute its fresh sample.

For the 5 arteries whose mechanical properties could not be characterised by the stress-strain curve, they were found to have abundant and localised calcifications on

visual inspection. Localised calcification made it difficult to achieve uniform tensile force and the artery were inclined to break near the regions of calcification. Moreover, the calcification caused stiffening of the arteries and the elasticity was compromised. As such, their experimental data had to be discarded.

This study also demonstrated that storage for up to 1 year in liquid nitrogen (-150°C) did not negatively affect the structural integrity of the artery. Minimal histological changes were noted for most of the specimen (Table 1). This finding is similar to that described by Rigol et al¹⁵ who noted that cryopreservation of arteries in liquid nitrogen could preserve endothelial function independent of storage time for up to 6 months. This was concluded as no interaction between the post-thawed arterial endothelium and platelet were detected on light microscopy.

In this study, the greatest amount of fragmentation was noted in areas of the arteries that had extensive atherosclerosis. Clinically, the presence of irreversible damage to the cryopreserved arterial wall could lead to failure of the arterial graft after implant.¹⁶ As such, for vascular tissue banks to obtain and store vascular grafts, the presence of atherosclerosis in donated arteries must be minimised. Suggested stringent exclusion criteria including a cap placed on donor's age and excluding patients with known atherosclerosis or known comorbidity such as hypertension, hypercholesterolemia and diabetes mellitus should be implemented. This is suggested as patients with the above-mentioned comorbidity is predisposed to accelerated atherosclerosis.²

In addition, this study suggests that cryopreservation may have a role in the sterilisation of vascular allograft. This is evident from the 2 vascular grafts (artery stored for 364 and 300 days) where though they had initial bacterial colonisation, no bacterial growth was detected in the post-thawed artery. For the other specimens, majority were negative for bacterial and fungal colonisation pre- and post-cryopreservation. One vascular graft (artery stored for 270 days) stood out as an outlier whereby bacterial growth was noted on its cryopreserved artery despite negative cultures initially. This could either be due to cross-contamination or the presence of a true bacterial growth. However, on the basis that sterility was maintained or improved in the other 11 vascular grafts, we suggest that from a microbiological point of view, cryopreserved arteries are safe for use as arterial allograft.

This study is limited as it provides limited insight into the degree of function that the tissue is capable of in vivo. Even with our newly developed mechanical testing apparatus, it can never fully replicate the physiological functioning of the vascular grafts. However, what we have used is a surrogate measure that has predicted a consistent mechanical

property between pre- and post-cryopreserved arteries. In addition, we were limited by the supply of human cadaveric arteries, hence were unable to assess the arteries stress-strain properties in a uniaxial circumferential direction or biaxial loading conditions. While we have only tested mechanical properties in a uniaxial longitudinal direction, this model of testing is regarded as an acceptable estimation when assessing arterial tissue.¹⁰ Through our study, we were thus able to evaluate the basic mechanical properties of the iliac arteries involved.

Also, as we were limited by the number of cadaveric iliac arteries, we had to settle on having only 1 sample at each time point. However, as this is an experimental and preliminary study, where we seek to investigate the effects of variable storage time for cryopreserved vessel, we decided to evaluate each vessel 30 days apart. Our study was thus better positioned to evaluate the trend of relative stiffness between pre- and post-cryopreserved vessel over a period of 1 year.

In addition, even though we set out to study the effects of the duration of cryopreservation on 12 arteries, we eventually had to exclude 5 arteries from our final analysis as these were arteries that had abundant calcification and could not undergo reliable mechanical testing. This is because, with localised calcifications, the tensile force distribution is not uniform. For example, some of the arteries were too stiff to be pulled and had hit the upper limit of our force sensor at low levels of strain. Similarly, due to calcification, some were characterised by premature breaks. Also, for the histological analysis, one sample (artery stored at 90 days) could not be assessed as it had incomplete section owing to tears present in the tissue. In addition, as the arteries did not undergo histological evaluation pre-cryopreservation, hence, for the arteries with extensive fragmentation, it cannot be concluded with certainty if its presence was due to the cryopreservation process. However, what is certain is that arteries with greater atherosclerosis have associated extensive fragmentation of the lumina elastica layers.

Long-term safety of cryopreserved arteries is determined by a multitude of factors such as haemodynamic properties, resistance to infection, anti-thrombotic properties, maintenance of vascular tone, immunologic properties and surgical technique.¹² This study does not extensively evaluate all these components. Further studies would need to be conducted to confirm the current hypothesis that cryopreserved arteries up to a year is a safe option for use as an arterial allograft.

Conclusion

In conclusion, histological and microbiological evaluation suggests that cryopreservation has little impact

on an artery structural integrity and may have a role in maintaining sterility and sterilising arteries from initial bacterial colonisation. Also, this preliminary study shows that mechanically non-atherosclerotic cryopreserved arteries can be a good substitute to its corresponding fresh arterial graft. However, the duration of storage does have an effect on their relative stiffness. A larger well designed experimental study that involves the collection of only non-atherosclerotic arteries and the mechanical assessment of pre- and post-cryopreserved arteries in uniaxial longitudinal, circumferential and biaxial loading conditions would be ideal in better characterising the mechanical properties of cryopreserved arteries.

Acknowledgements

The authors would like to thank A/Prof Krishnakumar Madhavan, Dr Iyer Shridhar Ganpathi and Dr Lee Tswen Wen Victor for their assistance in retrieving the arteries. The authors would also like to thank National Medical Research Council for their funding support.

REFERENCES

1. Castier Y, Leseche G, Palombi T, Petit MD, Cerceau O. Early experience with cryopreserved arterial allografts in below-knee revascularization for limb salvage. *Am J Surg* 1999;177:197-202.
2. Dominic P, Dodd F. What tissue bankers should know about the use of allograft blood vessels. *Cell Tissue Bank* 2010;11:3-11.
3. Bujan J, Pascual G, Lopez R, Corrales C, Rodriguez M, Turegano F, et al. Gradual thawing improves the preservation of cryopreserved arteries. *Cryobiology* 2001;42:256-65.
4. Muller-Schweinitzer E, Mihatsch MJ, Schilling M, Haefeli WE. Functional recovery of human mesenteric and coronary arteries after cryopreservation at -196 degrees C in a serum-free medium. *J Vasc Surg* 1997;25:743-50.
5. Rodriguez M, Pascual G, Perez-Kohler B, Cifuentes A, Garcia-Honduvilla N, Bellón JM, et al. Immune response to the long-term grafting of cryopreserved small-diameter arterial allografts. *Histol Histopathol* 2012;27:873-84.
6. Pascual G, Rodríguez M, Corrales C, Turégano F, García-Honduvilla N, Bellón JM, et al. New approach to improving endothelial preservation in cryopreserved arterial substitutes. *Cryobiology* 2004;48:62-71.
7. Venkatasubramanian RT, Grassl ED, Barocas VH, Lafontaine D, Bischof JC. Effects of freezing and cryopreservation on the mechanical properties of arteries. *Ann Biomed Eng* 2006;34:823-32.
8. He CM, Roach MR. The composition and mechanical properties of abdominal aortic aneurysms. *J Vasc Surg* 1994;20:6-13.
9. Pascual G, Jurado F, Rodríguez M, Corrales C, López-Hervás P, Bellón JM, et al. The use of ischaemic vessels as prostheses or tissue engineering scaffolds after cryopreservation. *Eur J Vasc Endovasc Surg* 2002;24:23-30.
10. Yang T, Chui CK, Yu RQ, Qin J, Chang SK. Quasi-linear viscoelastic modeling of arterial wall for surgical simulation. *Int J Comput Assist Radiol Surg* 2011;6:829-38.
11. Chui C, Kobayashi E, Chen X, Hisada T, Sakuma I. Combined compression and elongation experiments and non-linear modelling of liver tissue for surgical simulation. *Med Biol Eng Comput* 2004;42:787-98.

12. Gómez-Caro A, Martinez E, Rodríguez A, Sanchez D, Martorell J, Gimferrer JM, et al. Cryopreserved arterial allograft reconstruction after excision of thoracic malignancies. *Ann Thorac Surg* 2008;86:1753-61.
 13. McCready RA, Bryant MA, Divilbiss JL, Chess BA, Chitwood RW, Paget DS. Arterial infections in the new millenium: an old problem revisited. *Ann Vasc Surg* 2006;20:590-5.
 14. Delgadillo JOV, Delorme S, El-Ayoubi R, DiRaddo R, Hatzikiriakos SG. Effect of freezing on the passive mechanical properties of arterial samples. *J Biomedical Science and Engineering* 2010;3:645-52.
 15. Rigol M, Heras M, Martínez A, Zurbano MJ, Agustí E, Roig E, et al. Changes in the cooling rate and medium improve the vascular function in cryopreserved porcine femoral arteries. *J Vasc Surg* 2000;31:1018-25.
 16. Buján J, Pascual G, García-Honduvilla N, Gimeno MJ, Jurado F, Carrera-San Martín A, et al. Rapid thawing increases the fragility of the cryopreserved arterial wall. *Eur J Vasc Endovasc Surg* 2000;20:13-20.
-

Biological Reconstruction for Children with Osteosarcoma Around the Knee

Mark E Puhaindran,¹ MBBS, MRCS (Edin), MMED (Surg), Robert WH Pho,^{1,2} MBBS, FRCS, MD

Abstract

Introduction: Limb salvage in children with primary malignant bone tumours around the knee is challenging, with considerations such as shortening, bone and joint remodeling and high functional demands of active children. The ultimate aim for reconstruction is restoring a stable, painless and mobile joint. With improved survival rates from chemotherapy, reconstructive techniques should ideally last the child's lifespan. We adopted a biological approach by preserving the patients' native joint, with bony defects bridged by fibula grafts supplemented by autoclaved bone grafts infused with bone marrow. We conducted this retrospective review to determine if we were able to meet our objectives of reconstruction. **Materials and Methods:** A retrospective review of children with osteogenic sarcoma involving the distal femur or proximal tibia treated at our institution was done. Patients aged 13 years and below at the time of surgery who had undergone a limb salvage procedure that preserved the knee joint were included. **Results:** Nine patients were identified, 3 males and 6 females. The average age was 10.0 years (range, 7 to 13 years) at the time of surgery. Seven had tumours involving the distal femur while 2 had tumours involving the proximal tibia. There were no cases of local recurrence. Four of the 9 patients died from metastatic disease, the 5 surviving patients have no evidence of disease, and the average follow-up for survivors was 13.2 years. The average active range of motion for the knee joint was 96° (range, 50° to 130°). The average Musculoskeletal Tumour Society (MSTS) score was 26.3 (range, 23 to 30). **Conclusion:** We have observed this technique of limb salvage offers satisfactory limb function with long-term follow-up.

Ann Acad Med Singapore 2014;43:499-505

Keywords: Limb salvage, Malignant bone tumours

¹Department of Hand and Reconstructive Microsurgery, National University Hospital, Singapore

²Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: Dr Mark E Puhaindran, Department of Hand and Reconstructive Microsurgery, National University Hospital, 1E Kent Ridge Road, Level 11, NUHS Tower Block, Singapore 119228.

Email: mark_e_puhaindran@nuhs.edu.sg

Biological Reconstruction for Children with Osteosarcoma Around the Knee

Mark E Puhaindran,¹ MBBS, MRCS (Edin), MMED (Surg), Robert WH Pho,^{1,2} MBBS, FRCS, MD

Abstract

Introduction: Limb salvage in children with primary malignant bone tumours around the knee is challenging, with considerations such as shortening, bone and joint remodeling and high functional demands of active children. The ultimate aim for reconstruction is restoring a stable, painless and mobile joint. With improved survival rates from chemotherapy, reconstructive techniques should ideally last the child's lifespan. We adopted a biological approach by preserving the patients' native joint, with bony defects bridged by fibula grafts supplemented by autoclaved bone grafts infused with bone marrow. We conducted this retrospective review to determine if we were able to meet our objectives of reconstruction. **Materials and Methods:** A retrospective review of children with osteogenic sarcoma involving the distal femur or proximal tibia treated at our institution was done. Patients aged 13 years and below at the time of surgery who had undergone a limb salvage procedure that preserved the knee joint were included. **Results:** Nine patients were identified, 3 males and 6 females. The average age was 10.0 years (range, 7 to 13 years) at the time of surgery. Seven had tumours involving the distal femur while 2 had tumours involving the proximal tibia. There were no cases of local recurrence. Four of the 9 patients died from metastatic disease, the 5 surviving patients have no evidence of disease, and the average follow-up for survivors was 13.2 years. The average active range of motion for the knee joint was 96° (range, 50° to 130°). The average Musculoskeletal Tumour Society (MSTS) score was 26.3 (range, 23 to 30). **Conclusion:** We have observed this technique of limb salvage offers satisfactory limb function with long-term follow-up.

Ann Acad Med Singapore 2014;43:499-505

Keywords: Limb salvage, Malignant bone tumours

Introduction

Osteosarcoma is the most common primary malignant bone tumour in children. The most frequently affected joint is the knee, when tumours arise from the distal femur and proximal tibia.¹ Limb salvage is now widely accepted as an alternative to amputation to achieve local control of the tumour,^{2,3} and the feasibility of limb salvage is dependent on tumour biology, anatomical site, age and socioeconomic factors.

In children, limb salvage is compounded with the challenges of shortening, bone and joint remodeling and high functional demands of active children.⁴ The ultimate aim for reconstruction is the restoration of a mobile knee joint that is stable and painless. With the improved survival

rates from chemotherapy, reconstructive techniques should also be durable and long lasting, if possible, for the child's entire lifespan. In the reconstruction following resections for osteosarcoma around the knee joints of children, many centres have advocated methods such as rotationplasty,^{5,6} use of a growing prosthesis,⁷⁻⁹ allografts,¹⁰ epiphyseal distraction,¹¹ and distraction osteogenesis.¹² We have adopted a biological approach using a technique developed by the senior author.¹³ The patient's native knee joint (including the epiphysis or physis) was preserved. Large bony defects were bridged by fibula grafts supplemented by autoclaved bone grafts infused with bone marrow in order to achieve immediate stability, early weight bearing and rehabilitation.

¹Department of Hand and Reconstructive Microsurgery, National University Hospital, Singapore

²Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: Dr Mark E Puhaindran, Department of Hand and Reconstructive Microsurgery, National University Hospital, 1E Kent Ridge Road, Level 11, NUHS Tower Block, Singapore 119228.

Email: mark_e_puhaindran@nuhs.edu.sg

We conducted this retrospective review of patients children with osteogenic sarcoma of the distal femur and proximal tibia that were treated at our institution over the past 20 years in order to assess the long-term functional outcomes and durability of this technique.

Materials and Methods

A retrospective case note review of children with osteogenic sarcoma involving the distal femur or proximal tibia who were treated at our institution was done. Patients aged 13 years and below at the time of surgery who had undergone a limb salvage procedure that preserved the knee joint were included. Those who underwent primary amputation or arthrodesis of the knee joint were excluded. Assessment of the patients were done during clinic reviews, and findings presented are based on the latest visits. For patients that had succumbed to disease, the best scores were taken and recorded.

Functional assessment was done using the Musculoskeletal Tumour Society (MSTS) score,¹⁴ looking at 6 categories of pain, function, emotional acceptance, use of supports for walking and gait. A score of 0 to 5 was assigned to each category, with a score of 5 indicating the best function. The score was then added, with the highest possible score of 30. The active range of motion of the knee and limb length discrepancy were measured. For the surviving patients, we also asked their leisure activities, and noted the most physically demanding of these activities. Limb length discrepancy was also recorded, as well as the modifications required for coping with it.

Surgical Technique

All surgeries were performed by the senior author. The main criteria for joint preservation was the absence of intra-articular extension of the tumour on imaging, and the absence of an effusion. A good tumour response to preoperative chemotherapy was also essential for patients where the resection margin was expected to be close. This was assessed clinically by a decrease in the size of the swelling and pain from the tumour, and radiologically by increased ossification of the tumour seen on x-ray, decreased uptake on bone scan and a decrease of the oedema around the tumour on MRI.

In all cases, x-rays and MRI scans of the limbs and bone scans and computed tomography (CT) scans of the thorax were done before biopsy and after preoperative chemotherapy. CT scans of the legs were also done when necessary. Detailed imaging was essential to exclude trans-physeal and intra-articular extension (Fig. 1). At times, the margin of surgical resection had to be close to the tumour margin in order for the articular cartilage, sub-chondral

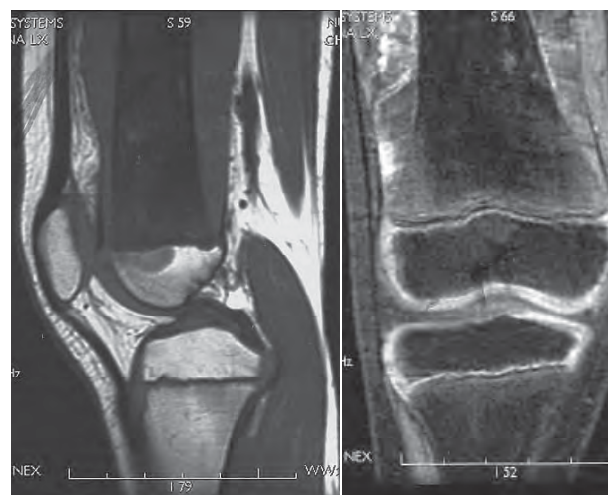


Fig. 1. MRI of the distal femur showing trans-physeal extension of the tumour (Patient 5).



Fig. 2. Photograph showing resection of the distal femur performed through the subchondral bone using an osteotome (Patient 5).

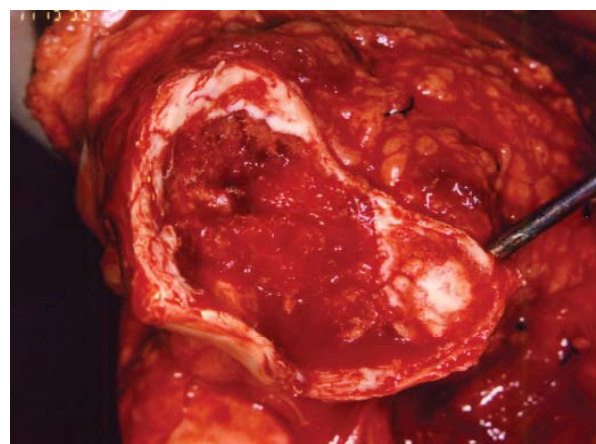


Fig. 3. Photograph showing the preserved subchondral bone and articular cartilage (Patient 5).

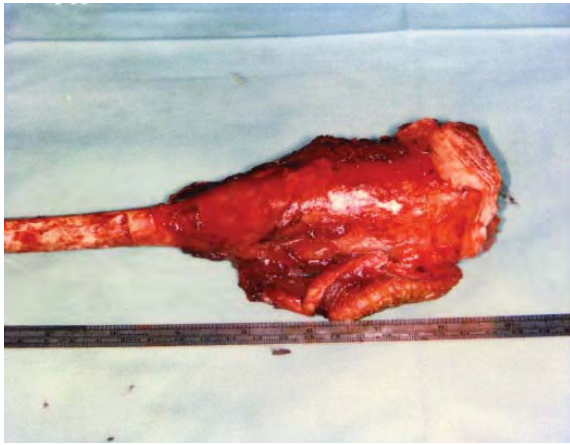


Fig. 4. Photograph showing the resected specimen. The tumour is then removed from the specimen on a separate table and the cortical bone autoclaved (Patient 5).

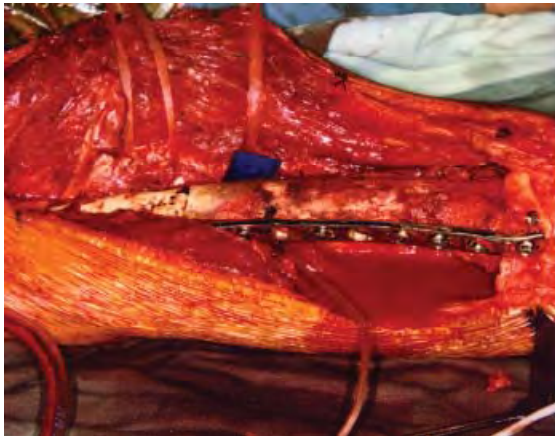


Fig. 5. Photograph showing the autoclaved bone with internal fixation done (Patient 5).



Fig. 6. Postoperative x-ray showing the fixation done for a distal femur tumour (Patient 5).

bone and ligaments to be preserved (Fig. 2).

At the start of surgery, iliac crest cortico-cancellous graft as well as bone marrow was harvested and stored. The donor site was then closed and dressed and re-draping was done. In patients with distal femur tumours, the fibular graft was harvested next and left on its vascular pedicle in situ. The ipsilateral fibular was used so that, in the event that the tumour recurred locally and amputation was required, there would be no donor morbidity affecting the contralateral normal limb.

Resection of the tumour was then performed, with the donor site sealed off. In proximal tibia lesions, resection was done prior to mobilisation of the ipsilateral fibular. Peri-articular resection was often performed using an osteotome (Fig. 2), allowing preservation of the articular cartilage, subchondral bone and ligaments that are critical to maintaining joint integrity and stability (Fig. 3).

The resected specimen was then brought to a separate table where the tumour and soft tissue were removed from the specimen and sent for histological assessment (Fig. 4). Sharp dissection was done using a knife to remove the soft tissue, while an osteotome was used to remove the osseous component of the tumour from the surface of the cortical bone. The bone was then placed in an autoclave and autoclaved at 132 degrees centigrade for 10 minutes before being removed. The harvesting of the fibular graft was then completed as the autoclaved graft cooled and closure of the donor site performed.

The cooled autoclaved graft was then infused with the harvested bone marrow and rigid internal fixation performed (Fig. 5). Fixation of the subchondral bone was always challenging, and at times had to be done using a combination of screws and staples (Figs. 6 and 7). The fibular graft was



Fig. 7. Postoperative x-ray showing the fixation done for a proximal tibia tumour (Patient 8).



Fig. 8. X-rays taken 5 years following surgery showing continued development of the right knee joint despite sacrifice of the physis (Patient 5).



Fig. 9. X-ray showing hypertrophy of the vascularised fibular graft with incorporation of the autoclaved graft with the host bone, together with a photograph showing the range of motion of the knee joint (Patient 3).

inset into a trough and fixed with screws proximally and distally. Microsurgical anastomosis was performed and the wound closed. We did not harvest the fibular graft with a skin paddle and assessment of viability was done with a bone scan at postoperative day 5. A backslab was then placed and converted to a full cast after one week. Protected weight bearing was allowed in the cast and full weight bearing only after bony fusion was seen at both ends. Chemotherapy was recommenced within 3 weeks of surgery. Those with lung metastases underwent thoracotomy and excision of the pulmonary metastases soon after the limb salvage procedure.

There were variations in the technique used in 3 patients. In patients 1 and 7, non-vascularised fibular grafts were used as it was felt that the good muscle bed could revascularise and support the graft.¹⁵ In patient 6, no autoclaved graft was used as it was too badly destroyed by the tumour and a vascularised fibular epiphyseal transfer was done instead to allow for growth.

Results

Nine patients were identified, 3 males and 6 females, and their average age was 10.0 years (range, 7 to 13 years) at the time of surgery. Seven of the patients had tumours involving the distal femur while 2 had tumours involving the proximal tibia. Also, 7 of them had Stage IIb disease while 2 had lung metastases at the time of diagnosis (1 distal femur, 1 proximal tibia).

There were no cases of local recurrence. Four out of the 9 patients died from metastatic disease, and the 5 surviving patients have no evidence of disease. The average follow-up from the time of surgery for survivors is 13.2 years (shortest 12 years, longest 16 years).

The average length of bone resected was 23.5 cm (range, 18.5 to 35 cm). The physis could be preserved in only one patient because it was involved with the tumour in the other patients. The largest limb length discrepancy was 10 cm, and this occurred in the 2 youngest patients with distal

Table 1. Patient Summary

No.	Age (years)	Sex	Site	Stage	Resection length	Growth plate	Surgery	Time to FWB	20 Procedures	Follow-up	Local recurrence	Oncologic outcomes	Limb shortening	MSTS score	Knee AROM	Recreational activities
1	13	F	DF	IIb	32 cm	Resected	NVFG + ABG	7 months	Nil	3 years	Nil	DOD 3 years	1 cm	25/30	0 – 900	NA
2	12	M	DF	IIb	18.5 cm	Preserved	VFG + ABG	11 months	Nil	12 years	Nil	CDF	Nil	30/30	0 – 1300	Running, basketball
3	11	F	DF	IIb	20 cm	Resected	VFG + ABG	9 months	Nil	18 months	Nil	DOD 18 months	Nil	30/30	0 – 1300	NA
4	8	F	DF	IIb	20 cm	Resected	VFG + ABG	9 months	Nil	4 years	Nil	DOD 4 years	6 cm	24/30	0 – 900	NA
5	7	F	DF	IIb	21 cm	Resected	VFG + ABG	9 months	Nil	12 years	Nil	CDF	10 cm	23/30	0 – 500	Walking
6	7	M	DF	IIb	21 cm	Resected	VFG (epiphyseal transfer)	17 months	1) Bone grafting, fixation revision 2) Limb lengthening	13 years	Nil	CDF	2.5 cm	24/30	0 – 600	Walking, kite flying
7	7	F	DF	III	24 cm	Resected	NVFG + ABG	24 months	Nil	6 years	Nil	DOD 6 years	10 cm	23/30	0 – 600	NA
8	13	M	PT	IIb	28 cm	Resected	VFG (pedicled) + ABG	11 months	Nil	13 years	Nil	CDF	1 cm	30/30	0 – 1300	Football, running
9	12	F	PT	III	27 cm	Resected	VFG (pedicled) + ABG	9 months	Sequestrectomy of infected ABG	16 years	Nil	NED (Metx)	Nil	28/30	0 – 1300	Walking, running

DF: Distal femur; PT: Proximal tibia; VFG: Vascularised fibular graft; NVFG: Non-vascularised fibular graft; ABG: Autoclaved bone graft; DOD: Died of disease; CDF: Continuously disease free; NED: No evidence of disease; Metx: Excision of metastasis; FWB: Full weight bearing; MSTS: Musculoskeletal Tumor Society Score; AROM: Active range of motion; NA: Not applicable

femur tumours that had the physis resected. However, we observed that while longitudinal growth is lost when the physis is sacrificed, latitudinal growth of the joint was still seen (Fig. 8).

The average active range of motion for the knee joint was 96° (range 50° to 130°) (Fig. 9). The average MSTS score was 26.3 (range, 23 to 30). Three of the 5 surviving patients were able to participate in running activities, while the others were able to swim and walk with a shoe raise, albeit with an altered gait. Some of the complications that we encountered included deep infection of the autoclaved graft in patient 9. There were fractures of the bone grafts in patients 6 and 7. Patient 6 was treated with revision of the fixation and bone grafting, while patient 7 was treated conservatively with prolonged casting. This resulted in a delay in return to full weight bearing for both patients. A summary of the results is presented in Table 1.

Discussion

We have found that biological reconstruction using autoclaved bone grafts infused with bone marrow that were reinforced with fibular grafts is a viable option in children with high grade osteosarcoma around the knee. It provides immediate stability, allowing early weight bearing and early rehabilitation. This construct is also durable, with none of our patients requiring revision surgery due to mechanical failure of the construct.

The disadvantage of this study is that it is a retrospective review of a small number of patients treated in a single centre. There were also different chemotherapy regimes used and not all patients underwent the exact same surgical procedure. However, the long period of follow-up has allowed us to demonstrate the durability of this construct.

Biological reconstruction is often technically more demanding than prosthetic replacement. Time to full weight bearing is longer than prosthetic replacement. However, once it works, the construct can be durable and further revision may not be required. Use of autoclaved bone grafts has the advantages of low cost, no rejection because the patient's own tissue is used, exact anatomical matching and no donor morbidity. The autoclaved bone, when infused with bone marrow, shows good bony union.¹³ Over time, the fibular hypertrophies and incorporates with the autoclaved graft (Fig. 4). However, when there is bone loss and extensive destruction in the pathological bone, then autogenous bone graft should be used to bridge and fill this area of bone loss. Two of our patients developed fractures of the graft, with one of our patients requiring revision of the construct and bone grafting (Patient 6), and another (Patient 7) requiring prolonged treatment with a cast. Patient 7 had a non-vascularised fibular graft placed and on retrospect, a vascularised fibular should have been

used instead. Patient 9 developed delayed deep infection of autoclaved tibia bone graft due to a prominent screw. She required repeated debridements and sequestrectomy of the infected autoclaved graft. However, the presence of vascularised graft allowed preservation of limb despite the infection due to its vascularity that made it resistant to infection.¹⁶ It eventually underwent hypertrophy and took over the weight bearing from the infected autoclaved graft that was removed.

This technique that we have developed has several advantages over implant arthroplasty—it does not require revision once bone healing is completed and it is affordable in many developing countries, avoiding the costs of megaprosthetic implants.⁷⁻⁹ It avoids the progressive wear and failure of osteoarticular allografts,¹⁰ and while rotationplasty does result in good functional outcomes,^{5,6} it is not culturally well accepted in our country. Other biological reconstructive techniques like distraction osteogenesis have also shown good results, though we have not adopted it in our practice because the physis has been shown as an inadequate barrier to local tumour spread,¹⁷ and there might be a higher risk of local tumour recurrence. In preserving the native joint, our margins of resection will be closer when compared with intra-articular resections, hence we have had to carefully selected cases for whom it was technically feasible and who had what we assessed was a good response to preoperative chemotherapy. We have managed to achieve negative resection margins and avoid local recurrence in this group of patients.

When the physis is preserved, the limb can be expected to grow. When surgery is done towards the end of the growing period, limb length equality can be maintained despite sacrifice of the physis, while a short discrepancy is easily tolerated and managed with a shoe raise. However, when the distal femur physis is sacrificed in younger patients, the final limb length discrepancy can be significant. We have observed that while longitudinal growth is lost when the physis is sacrificed, circumferential growth of the joint is still seen. Distraction osteogenesis can be done at the end of the growing period to correct significant limb length discrepancies.

Conclusion

We have observed this technique of limb salvage offers satisfactory limb function with long-term follow-up. One disadvantage is that this is technically demanding with resection performed close to the tumour margin, hence good preoperative assessment and good response to chemotherapy is essential. The use of vascularised fibular grafts and application of microsurgical anastomosis often poses a great challenge to many orthopaedic oncologists, but with an experienced team, this technique can be readily applicable in most orthopaedic oncology centres.

REFERENCES

1. Unni KK (ed): *Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases* ed 5. Philadelphia, PA: Lippincott-Raven, 1996.
2. Simon MA, Aschliman MA, Thomas N, Mankin HJ. Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. *J Bone Joint Surg Am* 1986;68:1331-7.
3. Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. A long-term oncological, functional, and quality-of-life study. *J Bone Joint Surg Am* 1994;76:649-56.
4. Futani H, Minamizaki T, Nishimoto Y, Abe S, Yabe H, Ueda T. Long-term follow-up after limb salvage in skeletally immature children with a primary malignant tumor of the distal end of the femur. *J Bone Joint Surg Am* 2006;88:595-603.
5. Hillmann A, Hoffmann C, Gosheger G, Krakau H, Winkelmann W. Malignant tumor of the distal part of the femur or the proximal part of the tibia: endoprosthetic replacement or rotationplasty. Functional outcome and quality-of-life measurements. *J Bone Joint Surg Am* 1999;81:462-8.
6. Hanlon M, Krajchich JJ. Rotationplasty in skeletally immature patients. Long-term followup results. *Clin Orthop Relat Res* 1999;358:75-82.
7. Schindler OS, Cannon SR, Briggs TW, Blunn GW. Stanmore custom-made extendible distal femoral replacements. *J Bone Joint Surg Br* 1997;79:927-37.
8. Eckardt JJ, Kabo JM, Kelley CM, Ward WG Sr, Asavamongkolkul A, Wirganowicz PZ, et al. Expandable endoprosthesis reconstruction in skeletally immature patients with tumors. *Clin Orthop Relat Res* 2000;373:51-61.
9. Henderson ER, Pepper AM, Marulanda G, Binitie OT, Cheong D, Letson GD. Outcome of lower-limb preservation with an expandable endoprosthesis after bone tumor resection in children. *J Bone Joint Surg Am* 2012;94:537-47.
10. Muscolo DL, Ayerza MA, Aponte-Tinao LA, Ranalletta M. Use of distal femoral osteoarticular allografts in limb salvage surgery. *J Bone Joint Surg Am* 2005;87:2449-55.
11. San-Julian M, Dölz R, Garcia-Barrecheguren E, Noain E, Sierrasesumaga L, Cañadell J. Limb salvage in bone sarcomas in patients younger than age 10: a 20-year experience. *J Pediatr Orthop* 2003;23:753-62.
12. Tsuchiya H, Abdel-Wanis ME, Sakurakichi K, Yamashiro T, Tomita K. Osteosarcoma around the knee. Intraepiphyseal excision and biological reconstruction with distraction osteogenesis. *J Bone Joint Surg Br* 2002;84:1162-6.
13. Taguchi Y, Pereira BP, Kour AK, Pho RW, Lee YS. Autoclaved autograft bone combined with vascularized bone and bone marrow. *Clin Orthop Relat Res* 1995;320:220-30.
14. Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. *Clin Orthop Relat Res* 1993;286:241-6.
15. Krieg AH, Hefti F. Reconstruction with non-vascularised fibular grafts after resection of bone tumours. *J Bone Joint Surg Br* 2007;89:215-21.
16. Low CK, Pho RW, Kour AK, Satku K, Kumar VP. Infection of vascularized fibular grafts. *Clin Orthop Relat Res* 1996;323:163-72.
17. Enneking WF, Kagan A 2nd. Transepiphyseal extension of osteosarcoma: incidence, mechanism, and implications. *Cancer* 1978;41:1526-37.

Natural History and Comorbidities of Subjects with Subclinical Hyperthyroidism: Analysis at a Tertiary Hospital Setting

Shaikh Abdul Kader Kamaldeen Abdul Shakoor, ¹MBBS, MD, MRCP (UK), Robert Hawkins, ²MBChB, MD, FRCPA, Shin Yii Kua, ²MBBS, Min Er Ching, ¹MBBS, Rinkoo Dalan, ¹MBBS, FAMS (Endocrinology), FRCP (Edinburgh)

Abstract

Introduction: Subclinical hyperthyroidism (SH, grade 1, thyrotropin (TSH) ≥ 0.1 mU/L and grade 2, TSH < 0.1 mU/L) is a common disorder with increased prevalence in older subjects. There is evidence for increased morbidities in SH, such as atrial fibrillation and osteoporosis. We aim to study the natural history and comorbidities of SH from patients referred to a tertiary endocrine clinic in Singapore as they are currently unknown. **Materials and Methods:** Retrospective evaluation of SH subjects for natural progression and comorbidities. **Results:** One hundred and thirteen SH subjects (male/female: 24/89, mean age: 67.2 years, grade 1/grade 2: 60/53) were identified from the endocrine clinic. The aetiology of SH include 52 multinodular goitre, 15 Graves' disease, 7 toxic adenoma and 39 unclassified. A minority of SH patients (5.3 %) progressed to overt hyperthyroidism while 13% remitted to euthyroid state (1 to 3 years with a mean follow-up of 18 months) in the total cohort. Most of the patients remained in SH state during follow-up (50/60 in grade 1 SH and 42/53 in grade SH). However, no single predictive factor could be identified for progression or remission of SH. The prevalence of morbidities in SH subjects include ischaemic heart disease (16.8%), heart failure (8.9%), tachyarrhythmias (13.3%), any cardiovascular disease (28%), cerebrovascular disease (28%), osteoporosis (28%), and any fracture (15.9%). **Conclusion:** Most of SH cases in our cohort remain in subclinical state with very few progressing to overt hyperthyroidism. Significant proportion of SH subjects have vascular disease, but this association needs to be confirmed in prospective controlled studies.

Ann Acad Med Singapore 2014;43:506-10

Key words: Cardiovascular risk, Progression, Remission

¹Department of Endocrinology, Tan Tock Seng Hospital, Singapore

²Department of Laboratory Medicine, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr SK Abdul Shakoor, Department of Endocrinology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

Email: shaikh_shakoor@ttsh.com.sg

Natural History and Comorbidities of Subjects with Subclinical Hyperthyroidism: Analysis at a Tertiary Hospital Setting

Shaikh Abdul Kader Kamaldeen Abdul Shakoor, ¹MBBS, MD, MRCP (UK), Robert Hawkins, ²MBChB, MD, FRCPA, Shin Yii Kua, ²MBBS, Min Er Ching, ¹MBBS, Rinkoo Dalan, ¹MBBS, FAMS (Endocrinology), FRCP (Edinburgh)

Abstract

Introduction: Subclinical hyperthyroidism (SH, grade 1, thyrotropin (TSH) ≥ 0.1 mU/L and grade 2, TSH < 0.1 mU/L) is a common disorder with increased prevalence in older subjects. There is evidence for increased morbidities in SH, such as atrial fibrillation and osteoporosis. We aim to study the natural history and comorbidities of SH from patients referred to a tertiary endocrine clinic in Singapore as they are currently unknown. **Materials and Methods:** Retrospective evaluation of SH subjects for natural progression and comorbidities. **Results:** One hundred and thirteen SH subjects (male/female: 24/89, mean age: 67.2 years, grade 1/grade 2: 60/53) were identified from the endocrine clinic. The aetiology of SH include 52 multinodular goitre, 15 Graves' disease, 7 toxic adenoma and 39 unclassified. A minority of SH patients (5.3 %) progressed to overt hyperthyroidism while 13% remitted to euthyroid state (1 to 3 years with a mean follow-up of 18 months) in the total cohort. Most of the patients remained in SH state during follow-up (50/60 in grade 1 SH and 42/53 in grade SH). However, no single predictive factor could be identified for progression or remission of SH. The prevalence of morbidities in SH subjects include ischaemic heart disease (16.8%), heart failure (8.9%), tachyarrhythmias (13.3%), any cardiovascular disease (28%), cerebrovascular disease (28%), osteoporosis (28%), and any fracture (15.9%). **Conclusion:** Most of SH cases in our cohort remain in subclinical state with very few progressing to overt hyperthyroidism. Significant proportion of SH subjects have vascular disease, but this association needs to be confirmed in prospective controlled studies.

Ann Acad Med Singapore 2014;43:506-10

Key words: Cardiovascular risk, Progression, Remission

Introduction

Subclinical hyperthyroidism (SH) is characterised by low serum concentration of thyrotropin (TSH) in the presence of normal serum thyroid hormones and the absence of obvious symptoms of hyperthyroidism. The reported prevalence of SH is variable (depending on the area, iodine intake, inclusion of exogenous SH), more common in women than in men (ratio of female: male is 1.5: 1) and its incidence increases with advancing age.¹ In the recent Cardiovascular Health Study (CHS) of 3233 American community-dwelling individuals aged 65 years or older, the prevalence of SH (TSH 0.10 to 0.44 mU/L) was 1.5%.² The prevalence of thyroid autonomy is inversely correlated with the population's iodine

intake.³ Singapore has been classified as an iodine-sufficient country by the World Health Organization (WHO) and International Council for the Control of Iodine Deficiency Disorders (ICCIDD).⁴ However the exact prevalence of SH in Singapore is currently not known.

The current management of SH is not consistent among endocrinologists and most of the patients are just monitored with regular thyroid function tests. Most of the reported studies including the recent ones showed that most SH patients remain in this clinical state for a longer duration with very few progressing to overt hyperthyroidism.⁵⁻⁷ Furthermore, it has been suggested that patients with grade 1

¹Department of Endocrinology, Tan Tock Seng Hospital, Singapore

²Department of Laboratory Medicine, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr SK Abdul Shakoor, Department of Endocrinology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

Email: shaikh_shakoor@tsh.com.sg

SH (serum TSH between 0.1 and 0.4 mU/L) rarely progress to overt hyperthyroidism as opposed to grade 2 SH (serum TSH <0.1 mU/L).⁵

SH is associated with increased cardiovascular morbidity, increased prevalence of supraventricular arrhythmias, and atrial fibrillation.^{2,8,9} A few but not all studies have shown increased vascular mortality in SH subjects.^{10,11}

The natural history and comorbidities of SH in the local Singapore population are unknown and hence we wished to evaluate the natural history of SH and prevalence of cardiac abnormalities (atrial fibrillation/other arrhythmias/cardiac failure/ischaemic heart disease), and other comorbidities such as reduced bone mineral density and fracture rates.

Materials and Methods

Potential SH patients were identified initially from the records of the laboratory medicine service at Tan Tock Seng Hospital (TTSH), Singapore, from October 2005 to January 2010, after local ethics committee approval was obtained. Serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were performed on 2 Beckman Coulter DxI-800 immunoassay analysers using manufacturer-supplied reagents and calibrators. Locally derived 95% reference intervals for each of the assays were FT4 8 to 21 pmol/L, FT3 4.3 to 8.3 pmol/L and TSH 0.34 to 5.6 mU/L.

Endogenous SH patients were identified from the initial list of patients who had low serum TSH and normal thyroid hormones (both FT4 and FT3). Patients on antithyroid drugs or levothyroxine and those who had low serum TSH due to non-thyroid illnesses were excluded. All patients on antithyroid drugs such as carbimazole or propylthiouracil given for overt hyperthyroidism or SH and those on levothyroxine supplement for hypothyroidism (obtained from TTSH pharmacy department or from medical records) were excluded. The medical records were then reviewed for natural progression of SH (by serial measurements of thyroid function after initial diagnosis of SH). The associated comorbidities, presence of ischaemic heart disease, atrial fibrillation, cerebrovascular disease, cardiac failure, reduced bone mineral density (BMD), and fracture was also reviewed from the medical records.

Statistical Analysis

This was done using statistical software STATA 11, (Texas, USA). The difference between groups was analysed using Student's t-test or Mann-Whitney U test (for not normally distributed data). Logistic regression analysis was done for factors predicting progression or remission of SH; factors evaluated include aetiology of SH, age at diagnosis, age > or <65 years, gender, TSH, FT4 and FT3 levels, grade of SH,

and size of the goitre. Similar factors were studied for the prediction of comorbidities such as presence of ischaemic heart disease, atrial fibrillation, cerebrovascular disease, any vascular disease and reduced BMD. A *P* value of <0.05 is defined for significant results between comparisons and for regression analyses.

Results

A total of 113 SH subjects (24 males and 89 females), mean age at diagnosis, $\pm$ SD 67.2 $\pm$ 17.7 years) were identified from the initial list of 6660 patients with biochemical SH. We have excluded patients with biochemical SH due to exogenous use of levothyroxine, those recovering from overt hyperthyroidism and those with transient SH state from non-thyroid illnesses. The prevalence of 3 common ethnicities in the total cohort is as follows: 98 (87%) Chinese, 6 (5%) Malay and 9 (8%) Indians. The aetiology of SH include 52 multinodular goitre (MNG), 15 Graves' disease (GD), 7 toxic adenoma (TA) and 39 unclassified. Sixty (53%) patients had grade 1 SH, whereas 53 (47%) had grade 2 SH at diagnosis. Clinical parameters in both grades of SH are summarised in Table 1.

Only 6 patients (5.3%) progressed to overt hyperthyroidism, while 15 remitted to euthyroid state on follow-up (1 to 3 years with a mean follow-up period of 18 months, 53 patients up to 2 years and 18 patients followed up to 3 years after diagnosis) in the whole study cohort. Figure 1 illustrates these progression/remission in both grades of SH. As this is a retrospective evaluation of patients followed by different clinicians, the follow-up was not uniform and some of the patients were lost to follow-up after a certain period. The progression to overt hyperthyroidism, remission to euthyroid state and persistence of SH in each grades of SH at 1 year, 2 years and 3 years is illustrated in Table 1. However, no single predictive factor (including initial TSH/FT4/FT3 levels, grade of SH, size of the goitre, diagnosis of SH and TSH receptor antibody levels) could be identified for progression (Table 2) or remission of SH.

The prevalence of morbidities in SH subjects include ischaemic heart disease (16.8%), heart failure (8.9%), tachyarrhythmia (13.3%), any cardiovascular disease (28%), cerebrovascular disease (28%), osteoporosis (28%), and any fracture (15.9%).

Subjects with FT4 >15 pmol/L predicted increased prevalence of any cardiovascular disease in logistic regression analysis, but became insignificant after adjusting for age.

Discussion

The natural history of patients with SH in Singapore appears to be similar to other clinical studies reported from

Table 1. Clinical Parameters in 2 Different Grades of Subclinical Hyperthyroidism

Characteristics	Grade 1 SH (n = 60)	Grade 2 SH (n = 53)	P value
Age (year)	68 ± 6.3	66 ± 19.3	0.3
Sex female (%)	45 (75%)	44 (83%)	0.2
Age >65 years (%)	38 (63%)	33 (62%)	0.4
TSH (mU/L)	0.21 ± 0.06	0.04 ± 0.02	<0.001
FT4 (pmol/L)	13.9 ± 2.6	15.4 ± 2.3	0.0008
FT3 (pmol/L)	4.8 ± 0.6	4.9 ± 1.9	0.4
Diagnosis of SH (%)			
MNG	30 (50%)	22 (42%)	
GD	6 (10%)	9 (17%)	
TA	2 (3%)	5 (9%)	
Unclassified	22 (37%)	17 (32%)	
Progression to overt hyperthyroidism at 1, 2 and 3 years	0/60, 1/28, 1/7*	4/53, 4/25, 4/11*	
Remission to euthyroid state at 1, 2 and 3 years	7/60, 2/28, 0/7*	4/53, 4/25, 3/11*	
Persistence of SH at 1, 2 and 3 years	53/60, 25/28, 6/7*	44/53, 18/25, 6/11*	

TSH: Thyrotropin, FT4: Free thyroxine, FT3: Free triiodothyronine, SH: Subclinical hyperthyroidism, MNG: Multinodular goitre, GD: Graves' disease, TA: Toxic adenoma

The values were provided in mean ± SD and P value of <0.05.

*Number of patients at different thyroid status/total number of patients followed at that time period.

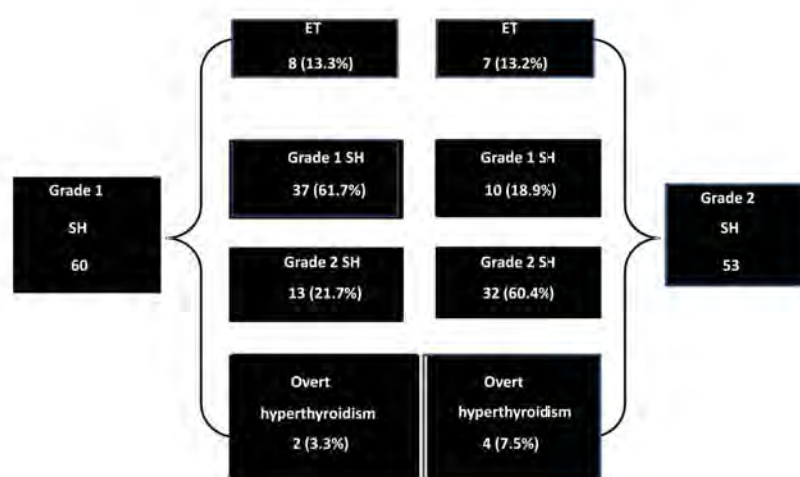


Fig. 1. Natural progression of SH in two grades of SH over 1 to 3 years period.
SH: Subclinical hyperthyroidism, ET: Euthyroid state

different geographical areas and iodine status. Furthermore, like previous published studies, we could not find any factors which could predict the progression of SH to overt hyperthyroidism or reversal to euthyroid state. We also found significant comorbidities in our SH patients such as cardiac problems (ischaemic heart disease, heart failure and atrial fibrillation), and cerebrovascular disease even though this could be an overestimate as this was evaluated in a tertiary care setting.

The progression of SH to overt hyperthyroidism was 5.3% in our SH cohort, which is rather similar to another retrospective study conducted in New Zealand.¹² Progression

to overt hyperthyroidism was seen in 8% at 1 year, 16% at 2 years, 21% at 3 years and 26% at 5 years in that study evaluating 96 consecutive SH patients. The rate of progression to overt hyperthyroidism may have been higher in our study, if we had followed our cohort for a longer period. However, in another large study from Dundee, UK (2024 SH patients), the rate of progression to overt hyperthyroidism was much lower (0.5 % to 0.7%) when followed up to 7 years after diagnosis of SH.⁷ The reason for the vast difference in the rate of progression could be due to the fact that both our study and the New Zealand study assessed SH patients at a secondary care setting with more

Table 2. Predictors for Progression of Subclinical Hyperthyroidism to Overt Hyperthyroidism over 1 to 3 Years Period

Factors	Odds ratio	Standard Error	P value	95% CI
Age at diagnosis	1.02	0.03	0.41	0.97 – 1.08
Age >65 years	3.1	3.5	0.3	0.35 – 27.53
Diagnosis of SH				
MNG	7.85	9.91	0.10	0.66 – 93.36
Graves' disease	8.50	12.57	0.15	0.47 – 154.17
Toxic adenoma	2.76	3.43	0.42	0.24 – 31.55
Initial TSH	0.42	0.37	0.3	0.07 – 2.41
Initial FT4	2.03	1.80	0.42	0.35 – 11.60
Initial FT3	0.97	0.66	0.97	0.26 – 3.68
TSH receptor antibody	2.04	1.86	0.44	0.33 – 12.3

SH: Subclinical hyperthyroidism, MNG: Multinodular goitre, TSH: Thyrotropin, FT4: Free thyroxine, FT3: Free triiodothyronine

frequent monitoring of thyroid function tests, whereas the Scottish study was done at a primary setting with possible less frequent monitoring. Furthermore, relative low iodine status in Scotland could also have contributed to the very low rate of progression in that study.

The majority of our SH patients remained in the SH state after follow-up period; 50 out of 60 grade 1 SH and 42 out of 53 grade 2 SH remained in SH state, which is similar to the Scottish study at 2 years after diagnosis. However, in that study, with a longer follow-up period, the less number of patients remained in SH state (67.5% at 5 years and 63% at 7 years).⁷ We did not follow longer than 3 years to compare our results to that Scottish study.

In the natural history of SH, the reversal back to normal euthyroid state has also been reported in previous studies. In our study, 8 out of 60 grade 1 SH and 7 out of 53 grade 2 SH patients reverted to euthyroid state. This finding is also rather similar to the Scottish study, which reported euthyroid reversal in 17.2%, 31.5% and 35.6% at 2, 5 and 7 years respectively.⁷ A higher number of grade 1 SH patients (38 out of 50) reverted to euthyroid state in another study from UK,⁵ but this could be due to the lack of strict criteria for diagnosing the SH state and possibility of including patients with non-thyroid illnesses, whereas we have included SH patients confirmed with 2 thyroid function tests at least 6 weeks apart.

The association of cardiac disease in SH such as increased basal heart rate, reduced variability of heart rate, atrial fibrillation and increased left ventricular mass has been confirmed in few studies and reviewed by Biondi and Cooper.⁹ The prevalence of atrial fibrillation in SH varies from 3.8%¹³ to 12.7%.⁸ The prevalence of tachyarrhythmia in our SH cohort was 13.3%, similar to 12.7% reported by Auer et al.⁸ A few but not all studies have reported increased risk of heart disease in SH patients. A total of 16.8% of our

SH patients had ischaemic heart disease, the prevalence of which is rather similar to the Scottish study (16.2%)¹³ even though the latter study is a population-based study whereas our study evaluated the prevalence of cardiac disease in a tertiary hospital setting. However, our estimation could be lower as we did not formally investigate them for the presence of ischaemic heart disease and collected information from the medical records and self-reporting in few patients.

We also found a significant proportion of cerebrovascular disease in our SH patients (28%). One Danish study also reported increased risk of stroke (hazard ratio of 3.39, CI, 1.15 to 10) in SH patients.¹⁴ Another recent study done in Germany reported 11.5% prevalence of SH in patients admitted with ischaemic stroke. The same study also reported that patients with SH had a substantial functional disability and poor outcome at 3 months after stroke compared to euthyroid subjects.¹⁵ However, the prevalence of SH was much lower (1.6%) in another South Korean study evaluating thyroid function in all consecutive ischaemic stroke patients.¹⁶ The last 2 studies (German and South Korean) assessed the prevalence of SH in patients admitted with stroke, whereas we have studied the prevalence of cerebrovascular disease including mild transient ischaemic attacks in SH patients, which could be the reason for higher prevalence of cerebrovascular disease in our cohort. The association of increased prevalence of cerebrovascular disease could also explain higher prevalence of cognitive dysfunction and dementia in SH patients reported in few studies.¹⁷ Hence, this association of cerebrovascular disease in SH needs to be confirmed in future prospective studies.

Our study is the first study evaluating a reasonable number of SH patients in a Singapore tertiary hospital representing all 3 common ethnicities and providing important clinical information in relation to natural history and comorbidities.

The disadvantages of our study include its retrospective nature, relatively shorter duration of follow-up of SH patients, assessment of comorbidities from medical records and hospital electronic system, which may have missed events that had happened in other hospitals elsewhere, and the possibility of overestimation of prevalence of associated comorbidities as this estimation was done in a tertiary hospital setting and hence cannot be generalised to the general Singapore population.

From the clinical perspective, our results confirm that most SH patients remain stable in SH state, but a significant number of patients have evidence of cardiovascular diseases such as ischaemic heart disease, atrial fibrillation and cerebrovascular disease as discussed above. Current joint guideline issued by American Thyroid Association and American Association of Clinical Endocrinologists (AACE/ATA) advocate treatment in selected SH patients depending on the age and serum TSH levels; treatment is suggested for those with TSH <0.1 mU/L if they are over 65 years of age, presence of heart disease, osteoporosis and the presence of hyperthyroid symptoms (almost all older grade 1 SH patients).¹⁸ We also agree with the above recommendations and at the moment there is no conclusive evidence of treatment benefit in younger SH patients, particularly those with grade 2 SH. However, as significant comorbidities have been found even in grade 2 SH patients and in younger patients, further studies are warranted in this cohort, particularly the effectiveness of treatment of SH state in relation to the cardiovascular outcome.

Conclusion

In summary, most of SH cases in our cohort remain in subclinical state with very few progressing to overt hyperthyroidism. Although a significant proportion of our SH subjects have vascular disease including cerebrovascular disease, this association needs to be confirmed in population-based and prospective-controlled studies. There is also a need to evaluate whether intervention by treatment of SH improves the vascular outcome.

REFERENCES

1. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489-99.
2. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 2006;295:1033-41.
3. Delange F, de Benoist B, Pretell E, Dunn JT. Iodine deficiency in the world: where do we stand at the turn of the century? *Thyroid* 2001;11:437-47.
4. Hetzel BS. Towards the global elimination of brain damage due to iodine deficiency – the role of the International Council for Control of Iodine Deficiency Disorders. *Int J Epidemiol* 2005;34:762-4.
5. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf)* 1991;34:77-83.
6. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. *Arch Intern Med* 1991;151:165-8.
7. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The thyroid epidemiology, audit, and research study (TEARS): the natural history of endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab* 2011;96:E1-8.
8. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J* 2001;142:838-42.
9. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 2008;29:76-131.
10. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA* 2004;292:2591-9.
11. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet* 2001;358:861-5.
12. Schouten BJ, Brownlie BE, Frampton CM, Turner JG. Subclinical thyrotoxicosis in an outpatient population – predictors of outcome. *Clin Endocrinol (Oxf)* 2011;74:257-61.
13. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The thyroid epidemiology, audit, and research study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab* 2011;96:1344-51.
14. Schultz M, Kistorp C, Raymond I, Dimsits J, Tuxen C, Hildebrandt P, et al. Cardiovascular events in thyroid disease: a population based, prospective study. *Horm Metab Res* 2011;43:653-9.
15. Wollenweber FA, Zietemann V, Gschwendtner A, Opherk C, Dichgans M. Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke. *Stroke* 2013;44:1446-8.
16. Jeong SK, Seo JY, Nam HS, Park HK. Thyroid function and internal carotid artery stenosis in ischemic stroke. *Endocr J* 2010;57:711-8.
17. Gan EH, Pearce SH. Clinical review: The thyroid in mind: cognitive function and low thyrotropin in older people. *J Clin Endocrinol Metab* 2012;97:3438-49.
18. Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract* 2011;17:456-520.

A Double-Blind, Randomised, Placebo-Controlled Trial of EMLA® Cream (Eutectic Lidocaine/Prilocaine Cream) for Analgesia Prior to Cryotherapy of Plantar Warts in Adults

Siew Hui Lee, ¹MSN, BSN, CCN, Janthorn Pakdeethai, ^{2,3}MBBS (Melbourne), MRCP(UK), MMed (Int Med), Matthias PHS Toh, ^{4,5}MBBS, MMed (Public Health), FAMS, Derrick CW Aw, ^{2,3}MRCP(UK), FAMS, GDA

Abstract

Introduction: Cryotherapy with liquid nitrogen is an effective, safe and convenient form of treatment for plantar warts. EMLA® cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is a topical local anaesthetic agent that has proven to be effective and well tolerated in the relief of pain associated with various minor interventions in numerous clinical settings. **Materials and Methods:** In a single-centre, double-blind, randomised placebo-controlled study, 64 subjects were randomised into 2 groups. The subjects had a thick layer of EMLA® cream or placebo cream applied to pared plantar wart(s) and onto the surrounding margin of 1 mm to 2 mm under occlusion for 60 minutes prior to receiving cryotherapy. The pain of cryotherapy was evaluated by the subjects using a self-administered Visual Analogue Scale (VAS) immediately after the cryotherapy. **Results:** There was no statistical difference between the mean VAS score for EMLA® cream (47.0 ± 21.4 mm) and placebo (48.9 ± 22.0 mm). Those with more than 1 wart had a significantly higher VAS score than those with only 1 wart (59.1 ± 21.8 vs. 44.3 ± 20.4 , $P < 0.05$) but this did not affect the therapeutic effect of EMLA® cream prior to cryotherapy. **Conclusion:** We conclude that the application of EMLA® cream prior to cryotherapy does not reduce the pain associated with cryotherapy.

Ann Acad Med Singapore 2014;43:511-4

Key words: Anaesthetic, Pain, Wart

¹Clinical Nursing Unit, National University Hospital, Singapore

²Division of Dermatology, Department of Medicine, National University Hospital, Singapore

³Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁴Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore

⁵Information Management, Corporate Development, National Healthcare Group, Singapore

Address for Correspondence: Dr Janthorn Pakdeethai, Division of Dermatology, Department of Medicine, National University Hospital, NUHS Tower Block, Level 10, Singapore 119228.

Email: janthorn_pakdeethai@nuhs.edu.sg

A Double-Blind, Randomised, Placebo-Controlled Trial of EMLA® Cream (Eutectic Lidocaine/Prilocaine Cream) for Analgesia Prior to Cryotherapy of Plantar Warts in Adults

Siew Hui Lee,¹ MSN, BSN, CCN, Janthorn Pakdeethai,^{2,3} MBBS (Melbourne), MRCP(UK), MMed (Int Med), Matthias PHS Toh,^{4,5} MBBS, MMed (Public Health), FAMS, Derrick CW Aw,^{2,3} MRCP(UK), FAMS, GDA

Abstract

Introduction: Cryotherapy with liquid nitrogen is an effective, safe and convenient form of treatment for plantar warts. EMLA® cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is a topical local anaesthetic agent that has proven to be effective and well tolerated in the relief of pain associated with various minor interventions in numerous clinical settings. **Materials and Methods:** In a single-centre, double-blind, randomised placebo-controlled study, 64 subjects were randomised into 2 groups. The subjects had a thick layer of EMLA® cream or placebo cream applied to pared plantar wart(s) and onto the surrounding margin of 1 mm to 2 mm under occlusion for 60 minutes prior to receiving cryotherapy. The pain of cryotherapy was evaluated by the subjects using a self-administered Visual Analogue Scale (VAS) immediately after the cryotherapy. **Results:** There was no statistical difference between the mean VAS score for EMLA® cream (47.0 ± 21.4 mm) and placebo (48.9 ± 22.0 mm). Those with more than 1 wart had a significantly higher VAS score than those with only 1 wart (59.1 ± 21.8 vs. 44.3 ± 20.4 , $P < 0.05$) but this did not affect the therapeutic effect of EMLA® cream prior to cryotherapy. **Conclusion:** We conclude that the application of EMLA® cream prior to cryotherapy does not reduce the pain associated with cryotherapy.

Ann Acad Med Singapore 2014;43:511-4

Key words: Anaesthetic, Pain, Wart

Introduction

Plantar warts are commonly diagnosed in dermatology clinics. They are painful, contagious and have the potential to cause considerable morbidity.¹ Among the therapeutic modalities, cryotherapy with liquid nitrogen is an effective, safe and convenient form of treatment for plantar warts.² However, therapeutic doses of liquid nitrogen can produce pain caused by the stinging sensation and the inflammation during the freezing cycle. It is not unbearable and usually short-lived. The wart will begin to turn white; this is a sign that the skin cells are dying. A blister may also form at the site of the wart. It is important to leave the blister alone; it will heal within a week.

EMLA® cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%), a topical local anaesthetic agent has proven to be effective and well tolerated in the relief of pain

associated with various minor interventions in numerous clinical settings.³⁻⁸ In the dermatology setting, studies on the effect of EMLA® cream to anaesthetise warts before cryotherapy were mainly confined to warts on non-hardened skin.^{9,10}

In a comparative study of children and adults, Gupta et al¹¹ found that EMLA® cream reduced pain over hardened skin (palms and soles) in children. To our knowledge, there have been no studies looking at the effectiveness of EMLA® cream to anaesthetise pared warts for liquid nitrogen cryotherapy in adults.

Our study aims to determine whether the application of EMLA® cream prior to cryotherapy could reduce the pain induced by cryotherapy.

¹Clinical Nursing Unit, National University Hospital, Singapore

²Division of Dermatology, Department of Medicine, National University Hospital, Singapore

³Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁴Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore

⁵Information Management, Corporate Development, National Healthcare Group, Singapore

Address for Correspondence: Dr Janthorn Pakdeethai, Division of Dermatology, Department of Medicine, National University Hospital, NUHS Tower Block, Level 10, Singapore 119228.

Email: janthorn_pakdeethai@nuhs.edu.sg

Materials and Methods

Study Design

The design was a single-centre, double-blind, randomised, placebo-controlled study on a single visit conducted in University Dermatology Clinic, National University Hospital of Singapore. Approval for the study was obtained from the national ethics committee.

Patient Selection

Patients with plantar warts for liquid nitrogen cryotherapy were potential candidates for the study. For inclusion into the study, the patient had to be at least 18 years old and capable of assessing pain using a visual analogue scale (VAS).¹² Both new and follow-up patient were eligible for the study as partially treated warts do not result in less pain caused by the mechanism of cold liquid nitrogen. Patients who had previously used EMLA[®] cream for cryotherapy of warts, known allergic sensitivity to EMLA[®] cream or amide type of local anaesthetic or with peripheral sensory neuropathy of both lower limbs were excluded from the study.

The primary outcome of the study was to explore the effect of EMLA[®] cream on levels of pain in adult patients with pared plantar warts receiving cryotherapy. The power of the study was estimated based on the primary outcome measure of VAS. In order to detect a difference of 25 mm in the pain scored on the VAS, assuming a standard deviation of 30 mm, 32 patients for each treatment arm could achieve 90% power at 5% level of significance.¹³

The subjects were randomly allocated by a computer-generated randomisation sequence into EMLA[®] cream or placebo group. Physiogel[™] cream was chosen as placebo as it was a conveniently available emollient most similar in colour and texture to EMLA[®] cream. It does not contain local anaesthetics. The assignments of subjects were concealed in sealed opaque envelopes. The randomisation codes and numbers were kept by a laboratory technician at the clinic. Both the subjects and the investigators were masked to group assignment. The randomisation code was unmasked at the end of the study by an assigned statistician.

Using a sharp blade, an investigator pared down the plantar warts of subjects till the texture of the lesion was as soft as the surrounding skin. A designated dermatology technician applied EMLA[®] cream or placebo cream as a thick layer to the warts and onto the surrounding margin of 1 to 2 mm. A transparent film dressing (Tegaderm[™] Film) was applied for 60 minutes. The cream was then removed and liquid nitrogen was applied for 5 to 10 seconds with double freeze-thaw cycles. The end-point of each freeze was a complete ice-ball covering the lesion with 1 to 2 mm peripheral extension. No oral analgesic was allowed prior to cryotherapy.

Assessment

Pain was evaluated using a self-administered VAS immediately after cryotherapy. The subjects were asked to mark their level of pain experienced during cryotherapy on a line from 0 to 100 mm. A score at 0 mm indicates no pain and 100 mm the most severe level of pain.

Statistical Methods

The data were analysed using PASW (version 19.0). Significance testing of proportions was carried out using chi-square test, and of means using t-test and analysis of variance (ANOVA), where a probability (*P*) of less than 0.05 was considered significant.

Results

A total of 41 male (64%) and 23 female (34%) patients were enrolled. The EMLA[®] cream and placebo groups were comparable with regard to age, gender and race (Table 1). Out of the 64 patients, 48 (75%) patients had 1 wart and the rest had more than 1 wart. The mean duration of wart in the EMLA[®] cream and placebo groups were 7.7 ± 1.9 and 7.9 ± 2.1 months respectively, and the mean size of the wart were 7.0 ± 4.3 mm and 6.7 ± 2.8 mm respectively. The majority (78.1%) had warts smaller than 10 mm in diameter.

The mean VAS score for EMLA[®] cream was 47.0 ± 21.4 mm and the placebo was 48.9 ± 22 mm. There was no statistical difference in the VAS score of cryotherapy between the 2 groups (Table 2). Analysis by gender showed the mean scores for men in the EMLA[®] cream and placebo groups to be 47.4 ± 21.7 and 46.0 ± 21.9 and female to be 46.4 ± 21.9 and 53.8 ± 21.9 respectively. There were no statistical differences in VAS scores between gender, duration and size of warts.

Younger non-Chinese participants, however, had a high mean VAS scores (51.2 ± 23 for age <25 years vs. 43.8 ± 19.4 mm for ≥ 25 years, $P < 0.05$; and 51.5 ± 21.4 for non-Chinese vs. 44.0 ± 21.4 mm for Chinese, $P < 0.05$). This is non-significant and can be due to the small sample size. There was a statistically significant difference in the mean VAS scores of patients with only 1 and more than 1 wart (44.3 ± 20.4 vs. 59.1 ± 21.8 mm, $P < 0.05$). This did not affect the conclusion regarding therapeutic effect of EMLA[®] cream prior to cryotherapy.

Discussion

Our study demonstrates that the application of EMLA[®] cream prior to cryotherapy to plantar warts does not reduce the pain associated with cryotherapy. The time and cost of EMLA[®] cream application may negate the statistically non-significant pain reduction during the treatment process. This

Table 1. Demographic Characteristics of the Study Population

Characteristics	Total (n = 64)			EMLA (n = 32)		Placebo (n = 32)	
	Number	%		Number	Row %	Number	Row %
Age (years)	<20	14	21.9	7	50.0	7	50.0
	21 – 30	26	40.6	15	42.3	11	57.7
	31 – 40	5	7.8	1	20.0	4	80.0
	41 – 50	6	9.4	2	33.3	4	61.7
	51 – 60	11	17.2	6	54.5	5	45.5
	61 and above	2	3.1	1	50.0	1	50.0
	mean ± SD	31.9 ± 14.9		31.4 ± 15.1		32.3 ± 14.9	
Gender	Male	41	61.1	21	51.2	20	48.8
	Female	23	35.9	11	47.8	12	52.2
Ethnicity	Chinese	30	46.9	13	43.3	17	56.7
	Non-Chinese	34	53.1	19	55.9	15	44.1
Number of warts	1	48	75.0	23	47.9	25	52.1
	2 or more	16	25.0	9	56.0	7	43.8
Size of warts (mm)	Less than 5	19	29.7	10	52.6	9	47.4
	5 – 9	31	48.4	14	45.2	17	54.8
	10 or more	14	21.9	8	57.1	6	42.9
	mean ± SD	6.9 ± 3.6		7.0 ± 4.3		6.7 ± 2.8	
Duration of warts (months)	Less than 6	36	56.3	18	56.3	18	56.3
	6 – 11	10	15.6	3	9.4	7	21.9
	More than 12	18	28.1	11	34.4	7	21.9
	mean ± SD	7.8 ± 1.4		7.7 ± 1.9		7.9 ± 2.1	

EMLA®: Eutectic mixture of lidocaine and prilocaine

Table 2. VAS Scores by Treatment Group

		Total (n = 64)	P value	EMLA [A] (n = 32)	Placebo [B] (n = 32)	P value [A] vs [B]
VAS	mean ± SD	48.0 ± 21.6		47.0 ± 21.4	48.9 ± 22.0	NS
Gender	Male	46.7 ± 21.6	NS	47.4 ± 21.7	46.0 ± 22.1	NS
	Female	50.2 ± 21.7		46.4 ± 21.9	53.8 ± 21.9	NS
Age Group (years)	Below 25	51.2 ± 23.0	NS	50.6 ± 21.8	54.0 ± 25.0	NS
	25 and above	43.8 ± 19.4		43.0 ± 21.0	44.4 ± 18.5	NS
Ethnicity	Chinese	44.0 ± 21.4	NS	41.2 ± 20.4	46.2 ± 22.5	NS
	Non-Chinese	51.5 ± 21.4		51.1 ± 21.7	52.0 ± 21.8	NS
Number of warts	1	44.3 ± 20.4	<0.05	45.2 ± 21.8	43.4 ± 19.4	NS
	2 or more	59.1 ± 21.8		51.7 ± 20.9	68.6 ± 20.6	NS
Size of warts (mm)	Less than 5	49.7 ± 17.4	NS	50.0 ± 16.0	49.4 ± 19.9	NS
	5 – 9	50.8 ± 24.9		50.0 ± 27.0	51.5 ± 23.9	NS
	10 or more	39.3 ± 17.2		38.1 ± 15.3	40.8 ± 20.8	NS
Duration of warts (month)	Less than 6	47.2 ± 23.5	NS	47.8 ± 23.4	46.7 ± 24.2	NS
	6 – 11	43.0 ± 20.8		35.0 ± 5.0	46.4 ± 24.4	NS
	12 or more	52.2 ± 18.0		49.1 ± 21.0	57.1 ± 11.9	NS

NS: Not significant; EMLA®: Eutectic mixture of lidocaine and prilocaine; VAS: Visual Analogue Scale

finding is in contrast to earlier studies. We postulate that the highly keratotic nature of plantar warts does not allow sufficient penetration of epicutaneously applied EMLA® cream despite pre-treatment paring. Based on the available evidence to date, EMLA® cream is likely an effective topical analgesia used to reduce pain in non-hardened, non-hyperkeratotic skin other than the palms and soles.

This study suggests sex differences in pain perception of cryotherapy. Women tend to have a lower pain threshold than men following the administration of cryotherapy. This may be associated with hyperalgesia in women and hypoactivity of the inhibitory system of pain in females.¹⁴ There are also sex differences in pain relieving effects of EMLA® cream. The poorer response of pain reduction following application of EMLA® cream in males could be the result of a thicker stratum corneum in males.¹⁵

The only significant finding from this study was that a lower pain threshold was observed in subjects with more than 1 wart. One would be more aggressive with pain control measures when using cryotherapy for patients with more than 1 wart.

Future studies can focus on alternative sites (non-palmoplantar), longer duration of EMLA® cream application, liposome-encapsulated lidocaine, a different topical local anaesthetic and a larger sample size.

Conclusion

The application of EMLA® cream prior to cryotherapy has no added benefit for reducing pain associated with cryotherapy. Other methods for achieving topical anaesthesia in cryotherapy of plantar warts should be explored.

Acknowledgements

The authors would like to thank the late Dr Teoh Chee Wei, Mdm Peh Bee Eng and all clinic assistants of University Dermatology Clinic for their technical assistance with the conduct of this trial.

REFERENCES

1. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. *Australas J Dermatol* 2003;44:169-73.
2. Buckley D. Cryosurgery treatment of plantar warts. *Ir Med J* 2000;93:140-3.
3. Akan A, Eryavuz Y, Kamali S, Simşek S, Hot S, Bademci R. A randomized, placebo controlled study: EMLA in minor breast surgery. *Minerva Chir* 2012;67:181-5.
4. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream. A review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). *Drugs* 1993;46:126-51.
5. Fransson J, Rönnerfält L, Wahlgren C F. EMLA cream provides rapid pain relief for the curettage of molluscum contagiosum in children with atopic dermatitis without causing serious application-site reactions. *Pediatr Dermatol* 1998;15:309-12.
6. Hallin A, Ljunghall K, Wallin J. Topical anaesthesia with local anaesthetic (lidocaine and prilocaine, EMLA) cream for cautery of genital warts. *Genitourin Med* 1987;63:316-19.
7. Monson J, Semaille C. Local anaesthesia of genital mucosa with a lidocaine/prilocaine combination cream before laser therapy of human papillomavirus lesions. *Eur J Dermatol* 2000;10:607-10.
8. Manner T, Kanto J, Iisalo E, Lindberg R, Viinamäki O, Scheinin M. Reduction of pain at venous cannulation in children with a eutectic mixture of lidocaine and prilocaine (EMLA cream): comparison with placebo cream and no local premedication. *Acta Anaesthesiol Scand* 1987;31:735-9.
9. Menter A, Black-Noller G, Riendeau LA, Monti KL. The use of EMLA cream and 1% lidocaine infiltration in men for relief of pain associated with the removal of genital warts by cryotherapy. *J Am Acad Dermatol* 1997;37:96-100.
10. Mansell-Gregory M, Romanowski B. Randomised double blind trial of EMLA for the control of pain related to cryotherapy in the treatment of genital HPV lesions. *Sex Transm Infect* 1998;74:274-5.
11. Gupta AK, Koren G, Shear NH. A double-blind, randomized, placebo-controlled trial of eutectic lidocaine/prilocaine cream 5% (EMLA) for analgesia prior to cryotherapy of warts in children and adults. *Pediatr Dermatol* 1998;15:129-33.
12. Tamiya N, Araki S, Ohi G, Inagaki K, Urano N, Hirano W, et al. Assessment of pain, depression, and anxiety by visual analogue scale in Japanese women with rheumatoid arthritis. *Scand J Caring Sci* 2002;16:137-41.
13. Chan YH. Randomised controlled trials (RCTs) – sample size: the magic number? *Singapore Med J* 2003;44:172-4.
14. Palmeira CC, Ashmawi HA, Posso Ide P. Sex and Pain Perception and Analgesia. *Rev Bras Anestesiol* 2011;61:814-28.
15. Sandby-Møller J, Poulsen T, Wulf HC. Epidermal thickness at different body sites: relationship to age, gender, pigmentation, blood content, skin type and smoking habits. *Acta Derm Venereol* 2003;83:410-3.

Open Reduction and Internal Fixation of Displaced Intra-articular Calcaneal Fractures with Norian Skeletal Repair System (SRS) Bone Cement: Surgical Technique, Clinical and Radiographical Results

Dear Editor,

The treatment of displaced intra-articular calcaneal fractures remains a topic of debate among orthopaedic surgeons.

In this study, we introduced a surgical technique for the treatment of displaced intra-articular calcaneal fracture with minimal hardware and Norian SRS bone cement. In addition, we also evaluated the cost-effectiveness of our technique.

Materials and Methods

This is a prospective review of patients with displaced intra-articular calcaneal fractures admitted to a Level 1 trauma centre under the care of a single primary trauma surgeon over a 1-year period from February 2010 to January 2011. A total of 9 patients with 11 closed calcaneal fractures were enrolled into the study. Only 1 calcaneal fracture per patient was treated.

Sanders classification was used to describe the fracture configuration and only type II and III calcaneal fractures were recruited.

Pre- and post-operative radiographic imaging was obtained to determine and monitor the Bohler's angle, Gissane's angle and talocalcaneal angles. All patients had preoperative computed tomography (CT) of the calcaneum to evaluate the fracture configuration.

Operative Technique

We employ the lateral extensile approach in all cases for open reduction and internal fixation. The full thickness fasciocutaneous flap, with the peroneal tendon and sural nerve, is elevated and two 2 mm Kirschner wires are inserted into the talus to retract the flap.

The lateral wall fragment is then elevated, revealing the degree of joint depression. Fracture depression is either reduced manually or with a lamina spreader under image intensifier guidance.

Four to five 1.6 mm non-threaded Kirschner wires are inserted in parallel from the posterior aspect of the plantar surface of the heel to reach the subchondral bone of the posterior facet. They function as a raft to maintain calcaneal height and aid in obtaining length and anatomical alignment.

The posterior facet is then reduced and compressed by the insertion of a 3.5 mm cortical lag screw, lateral to medial, into the sustentaculum tali.

Depending on the amount of bone void, 3 to 10 cm³ of Norian SRS bone cement are then inserted. Preparation of Norian SRS bone cement is according to the manufacturer's instructions and is injected via a delivery needle (Fig. 1).

The lateral wall fragment is then replaced and a 5-hole one-third tubular plate is used to buttress the lateral wall. Two fully threaded cancellous screws are inserted into the tubular plate, one into the most anterior hole directed toward the sustentaculum tali and another into the most posterior hole. Satisfactory anatomical reduction and anatomical alignment are verified with lateral and axial views obtained with the image intensifier. Figure 2 shows immediate post-operative X-ray images.

The 1.6 mm Kirschner wires on the heel are shortened and left exposed. The incision site is carefully closed in a tension-free fashion with interrupted subcutaneous and mattress skin sutures.

Postoperative Care

Kirschner wires were removed in clinic at 6 weeks postoperatively and full weight bearing commenced thereafter.

Results

There was no loss of reduction with respect to Bohler's angles, Gissane's angles and talocalcaneal angles except in 1 patient. However, we found no statistical significance ($P > 0.05$) between intraoperative angles and their corresponding angles on subsequent follow-ups for all patients, indicating no significant collapse of reduction.

On clinical assessment of postoperative axial alignment, all calcaneal bodies were restored to neutral or valgus alignment.

We utilised The American Orthopaedic Foot and Ankle Society (AOFAS) Ankle and Hindfoot Scale scoring system and Visual Analogue Scale (VAS) score to assess the functional outcome. Subgroup analysis revealed that



Fig. 1. Insertion of Norian SRS bone cement.

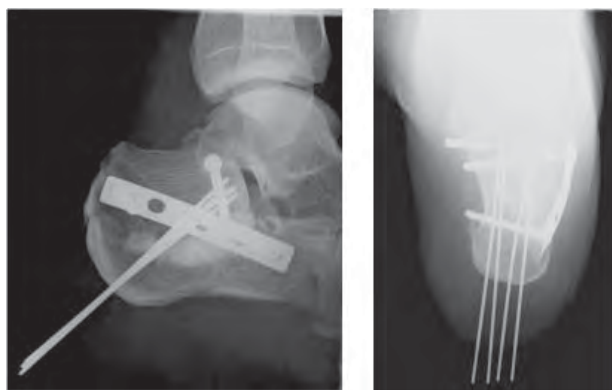


Fig. 2. X-ray images showing the insertion of Norian SRS bone cement.

patients who were receiving workmen compensation had a poorer functional score compared to patients who were not receiving workmen compensation.

Four patients were unable to return to work, all of whom were foreign workers under workmen compensation. Six patients complained of subjective subtalar ankle stiffness but only 1 of the 6 patients was confirmed with significant subtalar stiffness on clinical examination.

Discussion

Demcoe et al¹ used an extensile lateral approach with threaded Kirschner wire and a 5-hole one-third tubular plate for fixation. Alpha bone substitute material (α -BSM, DePuy) bone cement was used to fill the bone void. Kirschner wires were removed only at 12 weeks postoperatively and full weight bearing started thereafter.

We too, have utilised the extensile lateral approach and a 5-hole one-third tubular plate. However, we used non-threaded Kirschner wires and did not encounter any premature loosening or pin site infection. Norian SRS bone cement was used instead of α -BSM. In our series, Kirschner wires were removed at 6 weeks postoperatively and full

weight bear commenced thereafter, with no substantial collapse seen in our patients. We therefore recommend that threaded Kirschner wires are not required and that because of the compressive strength of Norian SRS bone cement, earlier weight bearing can be initiated using this technique.

Complications described by many other authors^{2,3} such as wound dehiscence, infections, tendon impingement, complex regional pain syndrome (CRPS), neuroma, tarsal tunnel syndrome, exostosis formation and revision operations were all not encountered in our series.

We also evaluated the cost-effectiveness of our technique. Using quotations given by local suppliers, the total estimated cost of the implants using a calcaneal locking plate with only locking screws is S\$720, compared with S\$395 for utilising our technique. There is a cost reduction of 55%.

Conclusion

We conclude that our method is an excellent and cost-effective technique for the surgical treatment of displaced intra-articular calcaneal fractures.

REFERENCES

1. Demcoe AR, Verhulsdonk M, Buckley RE. Complications when using threaded K-wire fixation for displaced intra-articular calcaneal fractures. *Injury* 2009;40:1297-301.
2. Buckley R, Tough S, McCormack R, Pate G, Leighton R, Petrie D, et al. Operative compared with nonoperative treatment of displaced intra-articular calcaneal fractures: a prospective, randomized, controlled multicenter trial. *J Bone Joint Surg Am* 2002;84:1733-44.
3. Sanders R. Displaced intra-articular fractures of the calcaneus. *J Bone Joint Surg Am* 2000;82:225-50.

Quan You Yeo, ¹MBBS (Singapore), Ernest BK Kwek, ¹FRCS
(Edinburgh) (Ortho), MMED (Ortho), MRCS (Edinburgh)

¹Department of Orthopaedic Surgery, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Quan You Yeo, Tan Tock Seng Hospital, Department of Orthopaedic Surgery, 11 Jalan Tan Tock Seng, Singapore 308433.

Email: yeoquanyou@gmail.com

Does Patient Education and Recommendation Result in Increased Uptake of Colorectal Cancer Screening Using the Fecal Occult Blood Test?

Dear Editor,

Colorectal cancer (CRC) is the most common cancer in Singapore. Between 2008 and 2012, it accounts for 17.5% of cancer in males and 13.6% in females.¹ Fecal occult blood test (FOBT) is a useful screening tool in decreasing CRC mortality.² A study conducted in Hong Kong, found that physician's recommendation had led to increased FOBT uptake among patients [odds ratio (OR) of 23.5%].³

This research study aims to determine whether patient education and recommendation would result in increased uptake of FOBT in polyclinics.

Materials and Methods

A randomised controlled study was conducted on 48 patients in a polyclinic to look at the effectiveness of a 3-minute standardised education protocol conducted by physicians. It compared the screening rates between the control group and intervention group on the uptake of FOBT among patients.

Study participants were randomised into 2 groups with balanced randomisation (1:1), using block randomisation. A research assistant screened and recruited patients according to the inclusion criteria. Concealment was performed by another research assistant who independently assigned group allocation using the pre-generated random allocation sequence. Both groups received CRC and FOBT public education materials. The intervention group additionally received a 3-minute standardised education protocol conducted by the doctor. Majority of the study participants were seen for review of their chronic illnesses; a few of them were for orthopaedic related conditions and upper respiratory tract illnesses. None of them consulted for gastrointestinal-related symptoms.

After the education, the doctor recommended FOBT and ordered 2 samples of FOBT tests if the patient accepted the offer. The laboratory technician, who was blinded to the patient allocation, recorded the time the patient had collected the kits. For Singapore citizens and Permanent residents, they would pay \$6.50 per kit; non-Singaporeans would pay \$11.80 per kit.

Both groups were followed up for 6 months after recruitment to determine if a FOBT was performed at the polyclinic.

Adults aged 50 years and above, and were asymptomatic for CRC were included. Patients were excluded if they had received an FOBT within 1 year; received a flexible sigmoidoscopy or colonoscopy within 5 years; a personal or family history of CRC or polyps; or a personal history of inflammatory bowel disease. Application to the National Healthcare Group (NHG) Domain Specific Research Board for ethical approval was obtained. Informed consent was taken from patients and participation was voluntary.

The education protocol included information on what is CRC and FOBT, the importance of CRC screening, how it is done, and its recommended frequency.

To detect an increase of FOBT rate from 3%⁴ to 40%,⁵ the minimum total sample size required was 40, with statistical power of 80% and significance level of 5%. Factoring in an anticipated loss to follow-up rate of 20%, the total number of subjects needed to be recruited was 48, 24 per group.

Intention to treat analysis was used. Descriptive statistics was used to summarise the data. Fisher's exact test was used to compare the baseline characteristics of the participants. The relative risk of screening take-up between control and intervention groups was computed and corresponding 95% confidence interval (CI) was reported. All analyses were performed using SPSS®.

Results

Out of the 48 participants, there was no significant difference in age and gender between the groups. Among the participants, 52.1% of them were aged between 50 and 60 years. The female to male ratio was 1:1.

In the intervention group, 14 out of 24 participants (58.3%) accepted the offer to take-up FOBT, 11 participants had the FOBT completed within 6 months (78.6%). Among the 10 participants who did not accept the offer, 1 had FOBT completed within 6 months (10%).

During the 6-month follow-up, as seen from Table 1, there was a total of 12 participants from the intervention group who completed the FOBT (50%). However, no participants from the control group completed the FOBT (0.0%). The rate of participants not undergoing a FOBT in the control group was twice as high as that of participants in the intervention group (RR = 2.0, 95% CI, 1.34 to 2.98)

Table 1. Return for FOBT Uptake and Participants' Characteristics

	Undergo FOBT		Did not undergo FOBT		RR of not undergoing FOBT	(95% CI)	P value
	Count	(%)	Count	(%)			
Group							<0.001
Control	0	(0.0%)	24	(100.0%)	2.00	(1.34 – 2.98)	
Intervention	12	(50.0%)	12	(50.0%)	1.00	(reference)	
Gender							1.000
Male	4	(16.7%)	20	(83.3%)	1.25	(0.89 – 1.75)	
Female	8	(33.3%)	16	(66.7%)	1.00	(reference)	
Age (years)							0.461
50 – 60	6	(24.0%)	19	(76.0%)	1.03	(0.74 – 1.43)	
>60	6	(26.1%)	17	(73.9%)	1.00	(reference)	

FOBT: Fecal occult blood test; RR: Relative risk

(Table 1). The rate of males not undergoing a FOBT was 1.25 times as high as that of females (RR = 1.25, 95% CI, 0.89 to 1.75). However, this association was not statistically significant. There was no significant association between the age and the FOBT take-up rate as well ($P = 0.868$).

Discussion

Data from this study suggest that patients were willing to return and take up FOBT with the education and recommendation provided by physicians.

Limitations

The study duration was short and the possibility of selection biases needs to be excluded. The sample size of this study was rather small and this would also limit the generalisability of the results.

Conclusion

This study reinforces the role of primary care physicians in advocating and encouraging patients to take up FOBT in colorectal cancer screening.

REFERENCES

1. National Registry of Diseases Office (NRDO), Singapore. Interim annual registry report – Trends in cancer incidence in Singapore, 2008-2012. Singapore Cancer Registry, 2013.
2. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993;328:1365-71.
3. Sung JJ, Choi SY, Chan FK, Ching JY, Lau JT, Griffiths S. Obstacles to colorectal cancer screening in Chinese: a study based on the health belief model. *Am J Gastroenterol* 2008;103:974-81.
4. Ministry of Health, Singapore. National Health Survey, 2010.
5. Frederiksen BL, Jorgensen T, Brasso K, Holten I, Osler M. Socioeconomic position and participation in colorectal cancer-screening. *Br J Cancer* 2010;103:1496-501.

Angelia HL Chua, ¹MBBS, MMed(FM), Gerald CH Koh, ²MMed(FM), MGer, PhD(FM)

¹Yishun Polyclinic, National Healthcare Group Polyclinics, Singapore

²Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore

Address for Correspondence: Dr Angelia Chua Hwee Ling, Yishun Polyclinic, National Healthcare Group Polyclinics, 30A, Yishun Central 1, Singapore 768796.

Email: hwee_ling_chua@nhgp.com.sg

Not All That Wheezes Is Asthma

A 62-year-old female complained of exertional dyspnoea associated with occasional wheeze over the past 10 years. She could not identify any trigger factors such as exposure to cold air, exercise or respiratory tract infections. She was treated empirically for bronchial asthma by her family physician with inhaled Salbutamol and inhaled Fluticasone without much relief in symptoms. She also recently complained of mild dysphagia on swallowing large boluses of food. There was no associated chest pain, weight loss or dyspepsia. The patient worked as a seamstress and was a non-smoker.

Physical exam was remarkable for expiratory wheeze, which was monophonic. Her voice was normal and there was no associated cervical adenopathy or goitre on neck examination. A flow-volume loop showed variable intrathoracic upper airway obstruction (Fig. 1A). Spirometry was normal. The chest radiograph is as shown in Figure 1B.

What is the diagnosis causing her symptoms?

- A. Intrathoracic goitre
- B. Paratracheal lymphadenopathy
- C. Aortic aneurysm
- D. Vascular ring
- E. Teratoma

The computed tomography scan of the chest (Fig. 2) confirmed a right-sided aorta associated with a diverticulum of Kommerell, an aberrant left subclavian artery and the left carotid artery forming a vascular ring. Bronchoscopy showed a mild stricture of the mid-trachea due to extrinsic compression. Therefore this patient has congenital vascular ring anomaly causing narrowing and displacement of the trachea and esophagus resulting in dyspnoea and dysphagia lusoria.

Discussion

Congenital anomalies of the great vessels are not uncommon, with a reported prevalence of between 0.5% and 1%.¹ They usually arise from incomplete or anomalous regression of the brachial arch system. These can occasionally lead to compression of the trachea and esophagus, especially when a vascular ring is formed as illustrated in this patient.

In our patient, a vascular ring surrounding the trachea and esophagus is formed by a right-sided aortic arch, the common carotid artery and a diverticulum of Kommerell together with an aberrant left subclavian artery (Fig. 2). A diverticulum of Kommerell is a pouch-like protrusion from the aortic arch and is formed by the persistence of the left fourth brachial arch during embryonic development.²

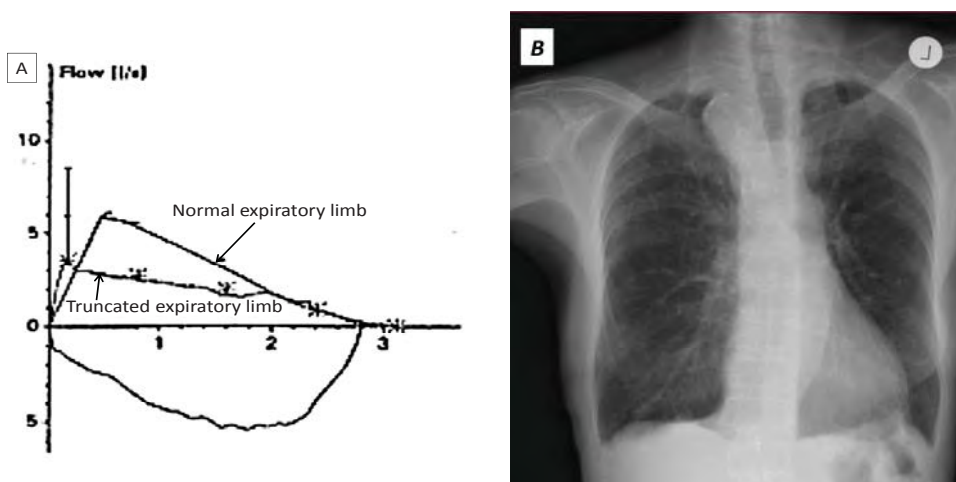


Fig. 1. At (A), chart of flow-volume loop showing truncation of the expiratory limb that is consistent with variable intrathoracic upper airway obstruction. At (B), right-sided aortic arch evident on the chest radiograph.

Answer: D

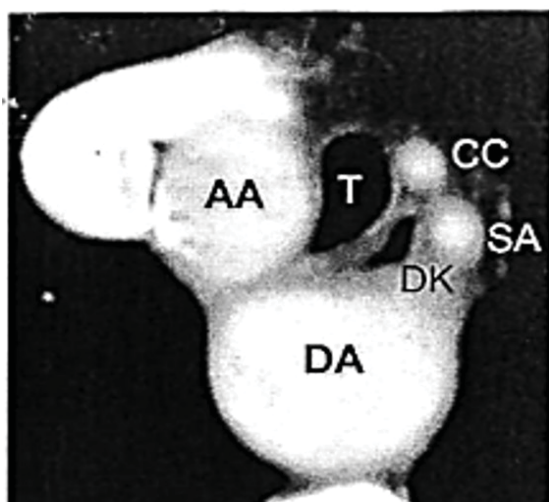


Fig. 2. Computed tomography showing an almost complete vascular ring surrounding the trachea and esophagus. The presence of a right-sided aortic arch, with aberrant left subclavian artery (SA), arising from the diverticulum of Kommerell, the adjoining esophagus being compressed by the aberrant SA resulting in dysphagia lusoria.

AA: Ascending aorta; DA: Descending aorta; SA: Subclavian artery (left); CC: Common carotid artery; DK: Diverticulum of Kommerell; T: Trachea

It usually gives rise to an aberrant left subclavian artery. Other vascular ring configurations have been described, including a right aortic arch with a persistent ligamentous arteriosum, a double aortic arch, an aberrant right subclavian artery and a pulmonary sling (an anomalous left pulmonary artery arising from the right pulmonary trunk which courses posteriorly between the esophagus and trachea).³

These anomalies usually present in childhood, with dysphagia, dyspnoea or wheeze.^{1,3,4} An adult presentation, especially presenting with both dyspnoea and dysphagia, is rare. Misdiagnosis as asthma⁵ and late development of esophageal compression from the vascular ring have been reported.⁶ Our patient had a few unusual clinical features for asthma, in that she had dyspnoea on exertion and dysphagia in the latter part of her presentation. The absence of paroxysmal episodes of wheeze with readily identified trigger factors as well as the lack of response to inhaled steroids and bronchodilators were also unusual. This case also highlights the importance of a chest radiograph and spirometry with a flow-volume loop, especially in patients with atypical features.

The management of a vascular ring varies according to the specific configuration but almost always involves surgical correction and division of the ring.^{1,4} It has been suggested that a diverticulum of Kommerell should always be excised, as there is a risk of rupture. Our patient had declined surgical correction as she deemed her symptoms to be mild and tolerable.

In conclusion, this case highlights the age-old adage that “not all that wheezes is asthma”. It is important to consider vascular ring anomalies, albeit rare, as a cause of dyspnoea and wheeze, especially in patients with aortic arch abnormalities on chest radiograph.

REFERENCES

1. Cordovilla ZG, Cabo SJ, Sanz GE, Moreno GF, Alvarez DF. Vascular rings of aortic origin: the surgical experience in 43 cases. *Rev Esp Cardiol* 1994;47:468-75.
2. Steiner RM, Wechler RJ, Granger RG. The thoracic aorta. In: Granger RG, Albion DJ, editors. *Diagnostic Radiology*. 2nd ed. New York: Churchill Livingstone, 1995.
3. Dillman JR, Attali AK, Agarwal PP, Dorfman AL, Hernandez RJ, Strouse PJ. Common and uncommon vascular rings and slings: a multi-modality review. *Pediatr Radiol* 2011;41:1440-54;quiz 1489-90.
4. Kir M, Saylam GS, Karadas U, Yilmaz N, Çakmakçı H, Uzuner N, et al. Vascular rings: presentation, imaging strategies, treatment, and outcome. *Pediatr Cardiol* 2012;33:607-17.
5. Parker JM, Cary-Freitas B, Berg BW. Symptomatic vascular rings in adulthood: an uncommon mimic of asthma. *J Asthma* 2000;37:275-80.
6. Nicolosi AC, Cambria RA. Late development of esophageal compression from a vascular ring. *Ann Thorac Surg* 1995;60:1413-5.

Serena LW Chong,¹ Anne AL Hsu,² MBBS (S'pore), FRCP (Edin.),

FAMS

¹Department of Medicine, The University of New South Wales, Sydney, Australia

²Department of Respiratory & Critical Care Medicine, Singapore General Hospital, Singapore

Address for Correspondence: Dr Anne AL Hsu, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, 20 College Road, Academia Level 3, Singapore 169856.

Email: gm3hal@sgh.com.sg