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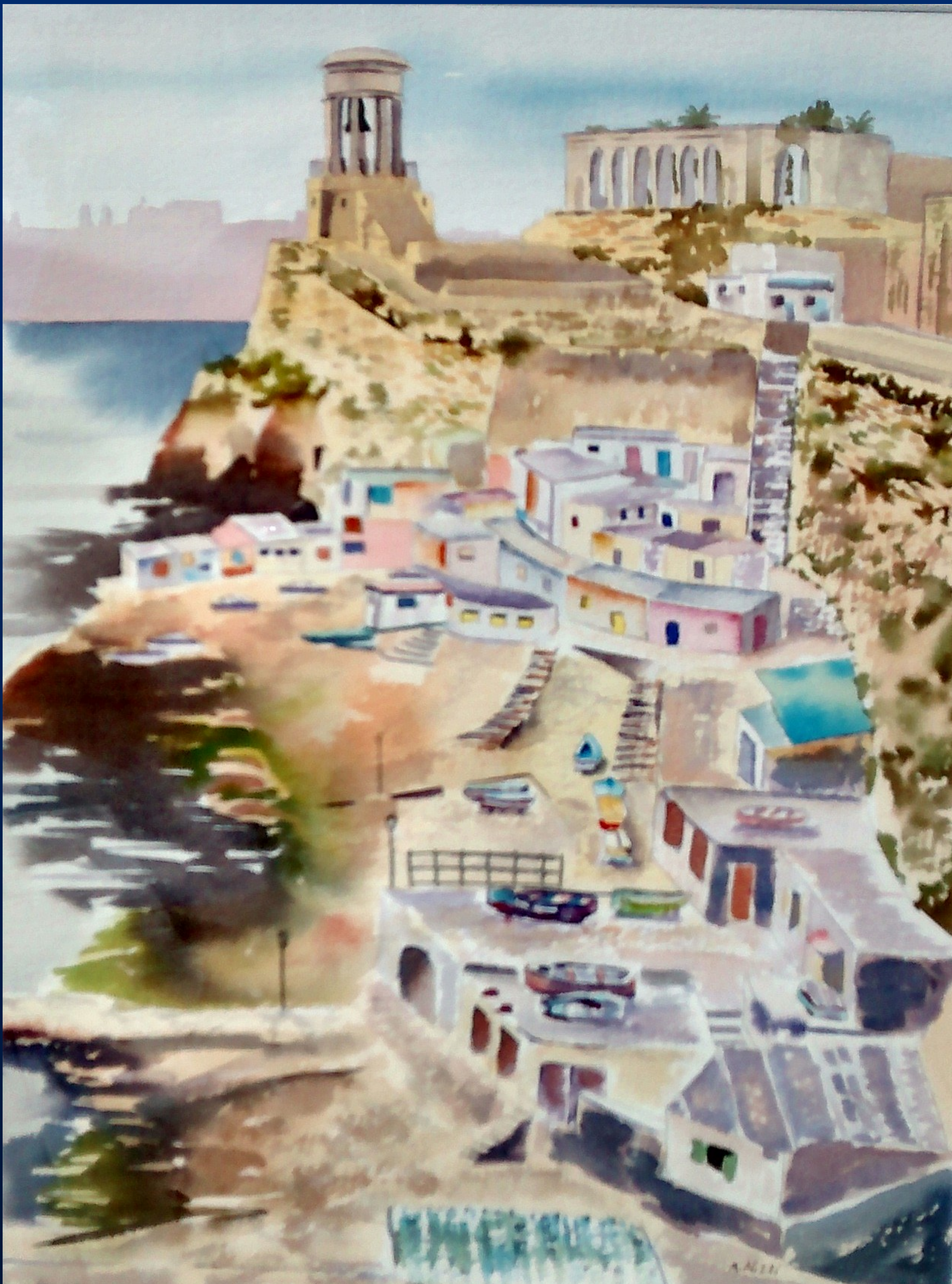

University of Malta
Medical School

UNIVERSITY OF MALTA
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Teenage pregnancy in Malta

Marcus Pace

The article by Grech et al highlights the need to reduce the number of teenage pregnancies in Malta. The difference in numbers between State and non-State schools is evident and warrants further studies. Is the discrepancy due to different teaching methods or does it reflect differences in socio-economic backgrounds? Sex education has always been a controversial topic and many parents have voiced concerns that too much information may encourage experimentation and promiscuity.

Sex education is an integral part of the school curriculum in many countries and to be effective must be part of a holistic program for health education, health promotion and life skills. According to the Canadian guidelines for sexual health education published in 2008, the goals should be two fold:

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i) To help young people achieve positive outcomes regarding self-esteem, respect for self and others, non-exploitive sexual relations, rewarding human relationships and informed reproductive choices;

ii) To avoid negative outcomes such as STDs, HIV, sexual coercion and unintended pregnancies.

Sexual health education methods vary and even in the U.S.A. there has been controversy over abstinence – only programs and abstinence – plus programs. The abstinence – plus program is also called the ABC approach: A- abstinence, B- be faithful and C- use a condom. In some American schools parents are asked to choose which program they would prefer for their children. Educating young people about contraceptives and whether or not these should be freely available is very controversial.

According to the World Bank, the global adolescent fertility rate (births per 1000 women aged 15-19 yrs) has fallen slightly from 46.5 in 2011 to 44.2 in 2015, the rates for Malta were 18 and 16/1000 respectively. The average rate for the E.U. was 13 in 2011 and 10/1000 in 2015. During the same period in the U.K. there was a drop from 20/1000 in 2011 down to 14/1000 adolescent women in 2015, this has been mainly due to better education and improved access to more sophisticated contraception. Due to the fact that the use of the combined oral contraceptive pill and the use of condoms has a significant failure rate amongst certain groups of adolescents, many family planning clinics in the U.K. and the U.S.A. have been promoting the use of long acting reversible contraceptives such as the IUCD and depot progestogen implants.

The availability and use of contraceptives by adolescents is an important issue for health care providers. The most vulnerable adolescents, notably from deprived areas will probably not use contraceptives on a regular basis unless they can get them free of charge, this has been noted both in the U.S.A. and the U.K. Whilst parental consent to prescribe contraceptives is not necessary in many Western countries, in other parts of the world this would be very controversial, more so if the young adolescent develops a complication such as deep vein thrombosis (from COCP) or has a uterine perforation (after insertion of IUCD).

As noted, teenage pregnancies are associated with increased risks for premature delivery, low birth weight and neonatal mortality. Lack of education and a deprived socio-economic background affects so many teenage mothers all over the globe. In Malta, a lot of work is being done to help these young mothers but there is always room for improvement. It is worth remembering that is some countries an unmarried pregnant woman would be considered to have an illegal pregnancy. The implementation of health promotion and sex education is improving but morals and religious beliefs must always be respected.

The article by Grech et al highlights an important problem and encourages further cooperation between the departments of health and education. I look forward to more studies in the future.

Editorial note

For the December 2017 issues and for all of 2018, the *Malta Medical Journal* and the *Malta Medical School Gazett*e will feature front covers that depict Valletta. This is in honour of Valletta 2018, wherein Valletta will be the European Capital of Culture, with all attendant programmes. The editorial board sincerely hopes that you will appreciate these covers as much as the actual contents.

Prof. Victor Grech

Cover Picture:
'Valletta boathouses'
Watercolour
By Adrian Mizzi

Adrian Mizzi is a consultant radiologist at Mater Dei Hospital, Malta. His special interests are chest and interventional vascular radiology. He studied medicine at University of Malta between 1990 and 1995 and pursued post-graduate training in radiology in Glasgow, UK between 1999 and 2005. He is post-graduate training coordinator for radiology and is the president of the Maltese Association of Radiologists and Nuclear Medicine Physicians.

Teenage pregnancy in Malta

Victor Grech, Miriam Gatt, Raymond Camilleri, Erin Camilleri, Neville Calleja

Abstract

Introduction: Underage pregnancy may blight a young woman's life. Teenage pregnancy rates vary widely across the world and have poorer pregnancy outcomes than non-teen pregnancies. Local Personal, Social and Career Development Education (PSCD) teaching is stipulated per curricula. This study was carried out by the Divisions of Education and Health in order to ascertain whether there are any differences in teenage pregnancy rates between State and non-State schools.

Methods: Ethical approval and data protection approval was obtained. The Health Division, identified pregnancies with mothers with age ≤18 years, for 2011-2015. Secondary schoosl attended were identified and an anonymised dataset was then passed on to the principal investigator for analysis.

Results: Teenage deliveries were significantly less in Non-State when compared to State schools, for each year studied, as well as for the aggregate of the total (p<0.0001). There was also a declining trend for teenage pregnancies in Non-State schools only (p=0.02).

Discussion: Abstinence-only sex education is a form of sex education that teaches abstinence from sex only. "Abstinence-plus" programs encourage sexual abstinence as the most effective means of HIV prevention and unwanted pregnancy avoidance, but also advocate condom use and partner reduction. It is suggested that the PSCD teaching methods in the different schools are compared as well as other factors that may further reduce teenage pregnancy.

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Introduction

Underage pregnancy may blight a young woman's life. Teenage pregnancy rates vary widely across the world and are known to be associated with poor antenatal attendance, smoking and a higher risk of spontaneous termination of pregnancy. They also have higher rates of perinatal mortality and morbidity due to higher rates of prematurity.[1-2] Local Personal, Social and Career Development Education (PSCD) teaching is stipulated per curricula albeit with possible variation due to different teaching methods.[3-5]

This study was carried out by the Divisions of Education and Health in order to ascertain whether there are any differences in teenage pregnancy rates between State and non-State schools. Any differences should be investigated and efforts would be focused on reducing such pregnancies to the lowest possible levels.

Methods

Ethical approval and data protection approval was sought from both Education and Health Divisions. The Health Division, via National Obstetric Information System (NOIS) at the Department of Health Information identified pregnancies with mothers with age ≤18 years, for the period 2011-2015. The Health Division, identified pregnancies with mothers with age ≤18 years, for 2011-2015. Secondary schools attended were identified as State/Non-State and an anonymised dataset was then passed on to the principal investigator for analysis.

Results

Deliveries for State and Non-State schools, as well as denominator data, calculated percentages and statistical testing are shown in table 1. Teenage deliveries were significantly less in Non-State when compared to State schools, for each year studied, as well as for the aggregate of the total.

There was also a declining trend for teenage pregnancies in Non-State schools only (chi for linear trend=5.8, p=0.02).

Table 1: *Deliveries for State and Non-State schools, annual denominator data, calculated percentages and statistical testing*

		2011	2012	2013	2014	2015	Totals
Teenage	**State**	67	47	42	33	47	236
Pregnancies	**Non-State**	13	7	8	8	2	38
Totals	**State**	7161	6885	6475	6122	5808	32451
	Non-State	4548	4582	4591	4488	4605	22814
Percentages	**State**	0.9	0.7	0.6	0.5	0.8	0.7
	Non-State	0.3	0.2	0.2	0.2	0.04	0.2
Statistical	**Chi**	17.3	16.5	13.4	8.8	32.2	85.4
Testing	**p**	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Discussion

Teenage pregnancies are associated with poorer outcomes than non-teenage groups. These include increased risks for premature delivery, low birth weight and neonatal mortality.[2] Furthermore, infants born to mothers aged ≤17 have a higher risk for low Apgar scores at 5 minutes.[2] These findings are independent of important known confounders such as age-appropriate education level, adequate prenatal care, and smoking and alcohol usage.[1]

Several factors may lead to teenage pregnancy and these include socio-economic background and lack of education.[1-2] Clearly, the only available avenue to attempt to reduce these pregnancy rates is education.

Abstinence-only sex education is a form of sex education that teaches abstinence from sex, while simultaneously often excluding other types of sexual and reproductive health education, particularly those focusing on contraception and safe sex. Education programs which focus exclusively on abstinence have hardly been shown to delay sexual activity.[6]

On the other hand, “abstinence-plus” programs (as opposed to abstinence alone) encourage sexual abstinence as the most effective means of HIV prevention and unwanted pregnancy avoidance, but also advocate condom use and partner reduction.[7]

A Cochrane review has shown that abstinence-plus programs reduce short-term and long-term HIV risk behaviour among youths in high-income countries. The programs were not shown to cause harm. This has critical implications for abstinence-based HIV prevention policies since abstinence-plus programs are likelier superior in prevention of disease and unwanted pregnancies.[7]

Local education programs that offer support and help to minors, their partners and their parents, within the Directorate for Educational Services, are varied and include (Mr. Raymond Camilleri – personal communication):

1. A specific program for pregnant young woman, meeting three times a week.
2. A support group for mother and baby meeting once a week.
3. Program of support for parents of young mothers and fathers.
4. Prevention programs for parents of children in all Secondary schools: State, Church and Independent.
5. Prevention programs for Form 3 students about physical relationships and sexual experimentation.
6. Outreach programs targettomg specific groups of students.
7. Information Meetings by specialists in the medical, legal, educational and social fields.
8. Counselling services for pregnant minors along with their partners and parents.
9. Programs that network with other bodies and agencies.

It is suggested that the PSCD teaching methods in the different schools are analysed and that an even greater emphasis is placed on abstinence-plus programs. The programs already in place, as listed above, appear more than adequate but perhaps more could be done, of a specific analytical nature. It might be possible to identify potential causes/precipitants for local teenage pregnancy in Malta in an attempt to further decrease the teenage pregnancy rate in this country.

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Original Article

Diagnosing lung malignancy from bronchoscopy in Malta – an update

Jonathan Gauci, Caroline Gouder, Peter Fsadni, Stephen Montefort

Abstract

Introduction: A previous local study by Agius *et al.* published in MMJ in 2009[1] identified a rise in lung adenocarcinoma over a decade, as well as an increasing number of females diagnosed with lung malignancy.

Aims and Objectives: The aim of this retrospective study was to further compare trends in lung malignancy diagnosis made from bronchoscopy in Malta to previous local data.

Materials and Methods: All bronchoscopies performed by one respiratory firm at Mater Dei Hospital in 2014-2015 were analysed, excluding those performed in intensive care. Cytology and histology results were retrieved and compared to those obtained from previously studied timeframes. Patients who had a post-bronchoscopy diagnosis via other means, were noted in order to calculate the bronchoscopy pick-up rate.

Results: 118 bronchoscopies were performed, 101 of which were done for suspected malignancy. 48 patients were diagnosed with lung malignancy from bronchoscopy in 2014-2015 by this respiratory firm. When compared to 2006-2007, 83.3% were males (vs 75%) and 16.7% were females (vs 25%). The overall bronchoscopy pick-up rate for malignancy was 81.4%. The most common histological diagnoses, when compared to 8 years previously, were adenocarcinoma 35.4% vs 27.8% (males 37.5% vs 31%; females 25% vs 14.3%), squamous cell 35.4% vs 44.4% (males 37.5% vs 44.8%; females 25% vs 42.9%), and small cell 14.6% vs 13.9%.

Conclusion: Lung adenocarcinoma has shown an upward trend in both gender groups, having now reached a similar prevalence to squamous cell carcinoma, which appears to be decreasing in both males and females in the Maltese population.

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Keywords

Lung Neoplasms, Bronchoscopy, Malta

Introduction

Worldwide trends in primary lung malignancy have shown a rise in adenocarcinoma. This is now the most common histological subtype worldwide[2], surpassing squamous cell which was historically the most frequent.

A 2009 Maltese study[1] compared trends in bronchoscopic findings over a decade by studying three 2-year periods: 1995-1996, 1999-2000 and 2006-2007. The study identified a local rise in adenocarcinoma reflecting international statistics; however squamous cell carcinoma remained the most common subtype.

International trends indicate a rising incidence of lung cancer in women. The 2009 local study also revealed an increasing number of females diagnosed with lung malignancy over a decade.

This 2014-2015 local project aimed to study the bronchoscopic diagnoses of lung cancer and compare them to the data from 1995-1996, 1999-2000 and 2006-2007, and to identify whether local data shadows worldwide trends in the rise of lung adenocarcinoma.

Materials and Methods

Inclusion and Exclusion Criteria

All patients who had a flexible bronchoscopy at Endoscopy Unit, Mater Dei Hospital under the care of one respiratory physician between January 2014 and December 2015 were included in the study. Patients who had a bronchoscopy in the Intensive Therapy Unit were not included.

Data Collection

Patient gender, age, smoking history and presenting symptoms were recorded from the bronchoscopy reports. The presence or absence of macroscopic abnormality on bronchoscopy was also recorded from the bronchoscopy sheet. The pre-bronchoscopy Chest X-rays and Computed Tomography (CT) scans were reviewed on Picture Archiving and Communication System (PACS®) and the results were noted.

The presence or absence of sputum studies, bronchial washings, bronchial brushings and endobronchial biopsies was noted from iSoft Clinical Manager®. The final cytology or histology outcome was recorded for each patient, and the availability of immunohistochemistry was documented.

Patients who had a post-bronchoscopy cancer diagnosis via other means such as radiologically-assisted biopsy and surgery, were also noted in order to calculate the bronchoscopy pick-up rate.

Data Analysis

The data for malignancy patients was compared with those from a similar study recording malignancy data from 1995-1996, 1999-2000 and 2006-2007.

Results

A total of 118 bronchoscopies were performed by one respiratory firm between January 2014 and December 2015, 101 of which were done for suspected malignancy. Of these, 48 (46.7%) had a malignant diagnosis from bronchoscopy.

Demographics

The mean age of our cohort with lung malignancy was 67 years, with a range of 49 to 87, and a median of 67.5 years. 40 patients (83.3%) were male, and the remaining 8 (16.7%) were female. Fig. 1 shows the trends in gender ratio, in comparison with previous local data.

Smoking History

Of the patients diagnosed with malignancy from bronchoscopy, 23 patients (47.9%) were current smokers, 17 (35.4%) were ex-smokers, 7 (14.6%) were non-smokers, and the remaining patient had no smoking history documented. Fig. 2 shows the trends in smoking history in males and females separately over the past two decades.

***Figure 1**: Gender Distribution of Malignancy Patients*

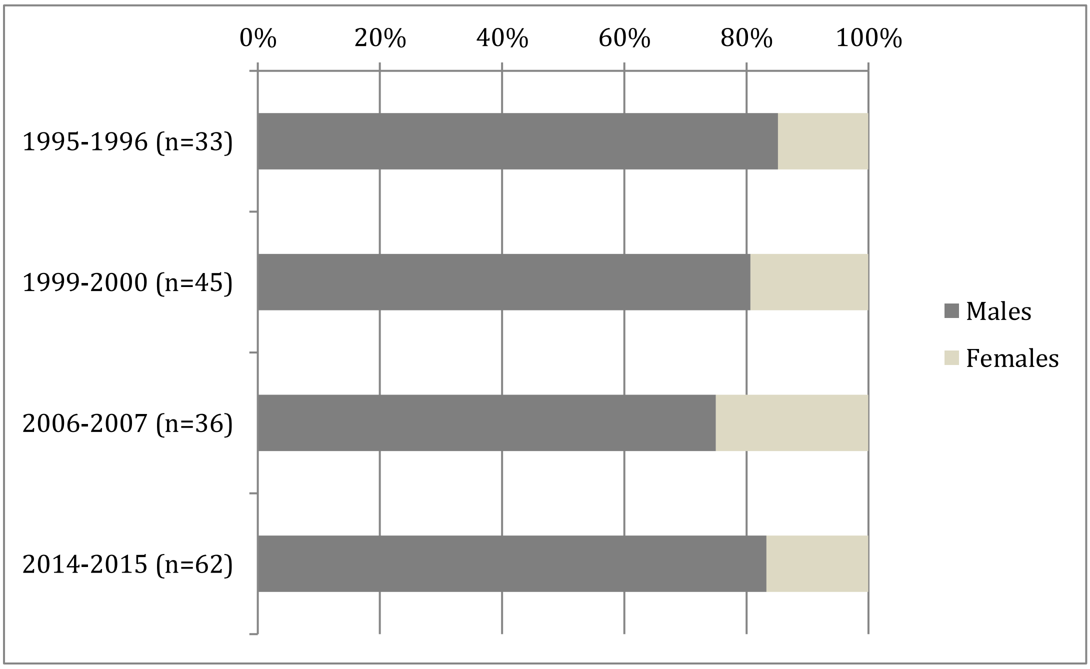


***Figure 2:** Smoking History of Malignancy Patients*

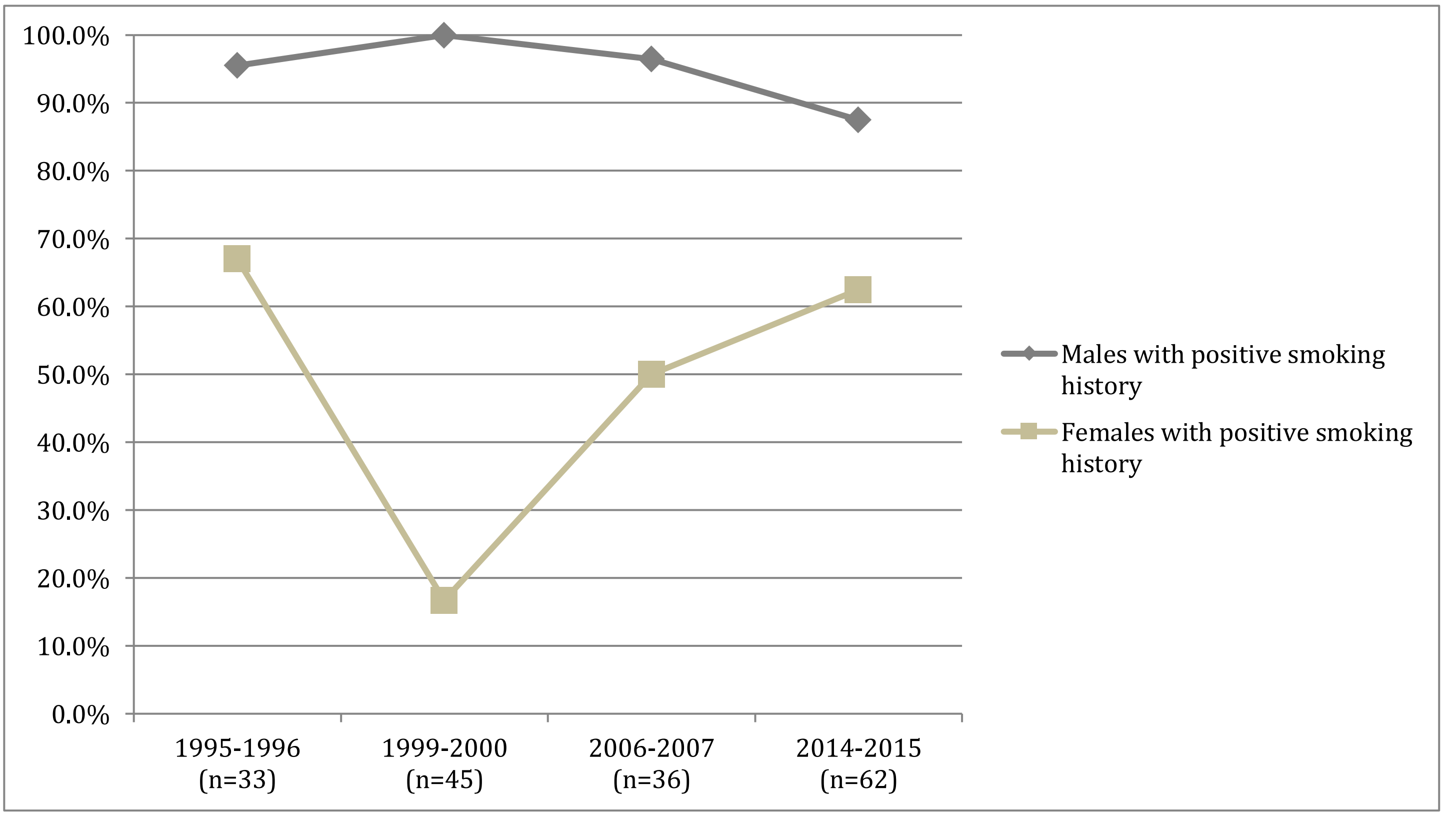
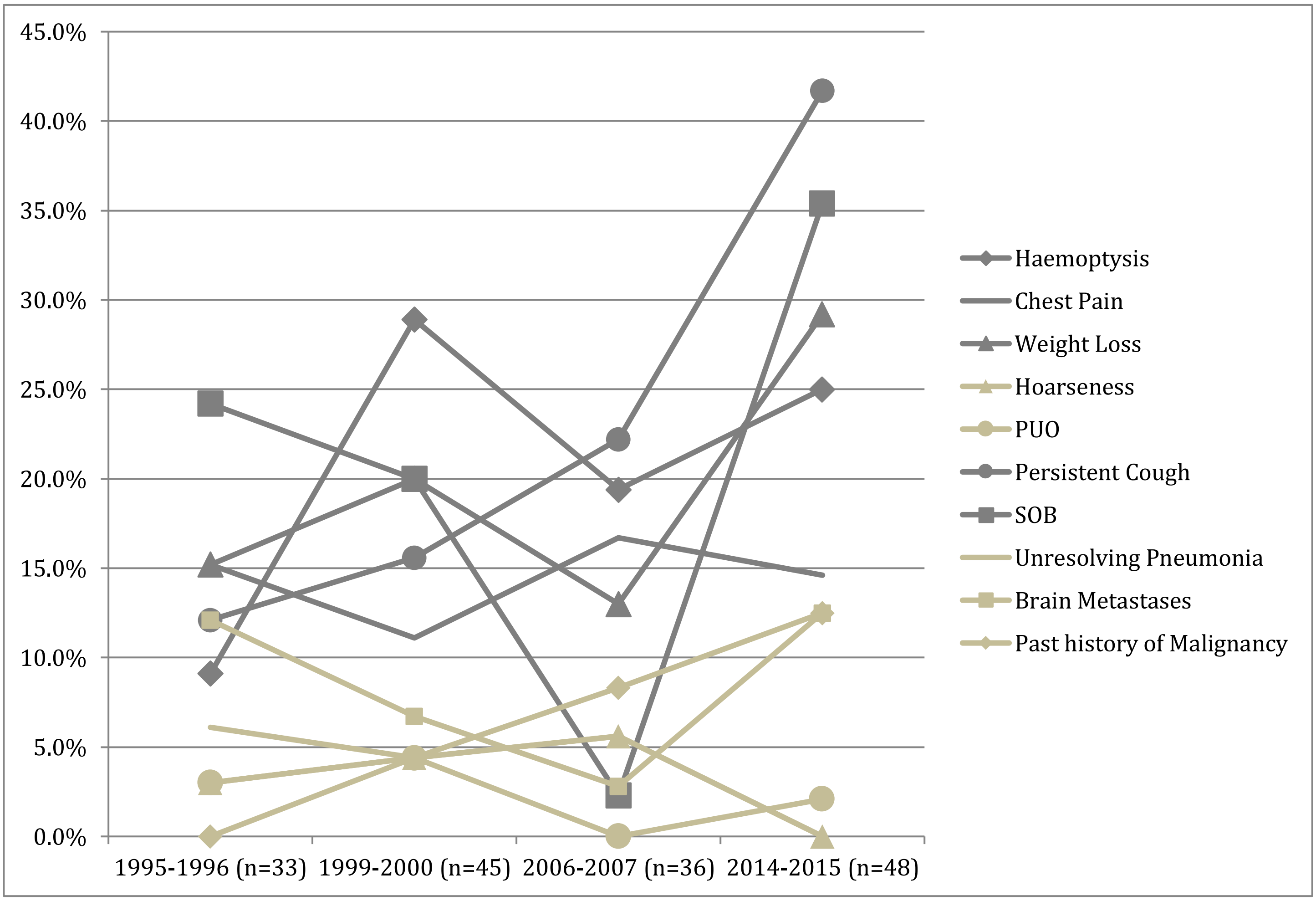


***Figure 3**: Presenting Symptom of Malignancy Patients*



Symptoms

Fig. 3 shows the trends in presenting complaint, in comparison with previous data. Persistent cough was the most common presenting symptom in the 2014-2015 cohort, followed by shortness of breath.

Imaging results

42 patients (89.6%) had a documented abnormal chest X-ray prior to bronchoscopy. 1 patient had a normal X-ray, while 4 patients did not have a chest X-ray. All patients had an abnormal pre-bronchoscopy CT thorax.

Sputum yield

Sputum studies were largely unreliable since many samples were sub-optimal. 5 patients (10.4%) had a malignancy diagnosis from sputum cytology.

Bronchoscopic yield (Figs. 4 and 5).

Of the patients diagnosed with malignancy from bronchoscopy, 44 patients (91.7%) had a macroscopic abnormality on bronchoscopy, while the remaining 4 (8.3%) had a macroscopically normal bronchoscopy. All patients had bronchial washings or lavage taken, and 40 were positive. The positive yield of bronchial washings when considering those patients who had a malignant diagnosis made from bronchoscopy was therefore 83.3% (40 out of 48). All patients had bronchial brushings taken, 39 of which were positive. The positive yield of bronchial brushings when considering those patients who had a malignant diagnosis made from bronchoscopy was 81.3% (39 out of 48). 35.4% (17 patients) had an endobronchial biopsy, of which 13 were positive. The positive yield of endobronchial biopsy when considering those patients who had a malignant diagnosis made from bronchoscopy was 76.5% (13 out of 17).

Figure 4: *Bronchoscopic Procedures Performed*

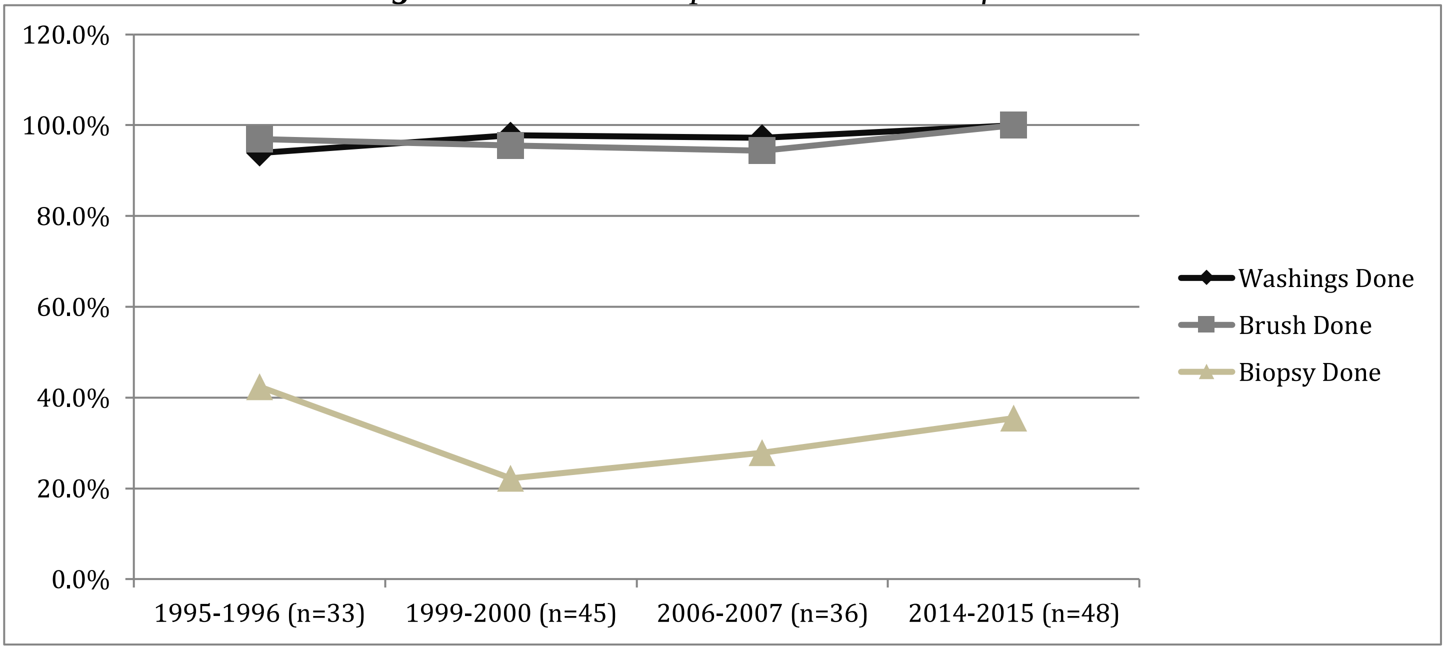
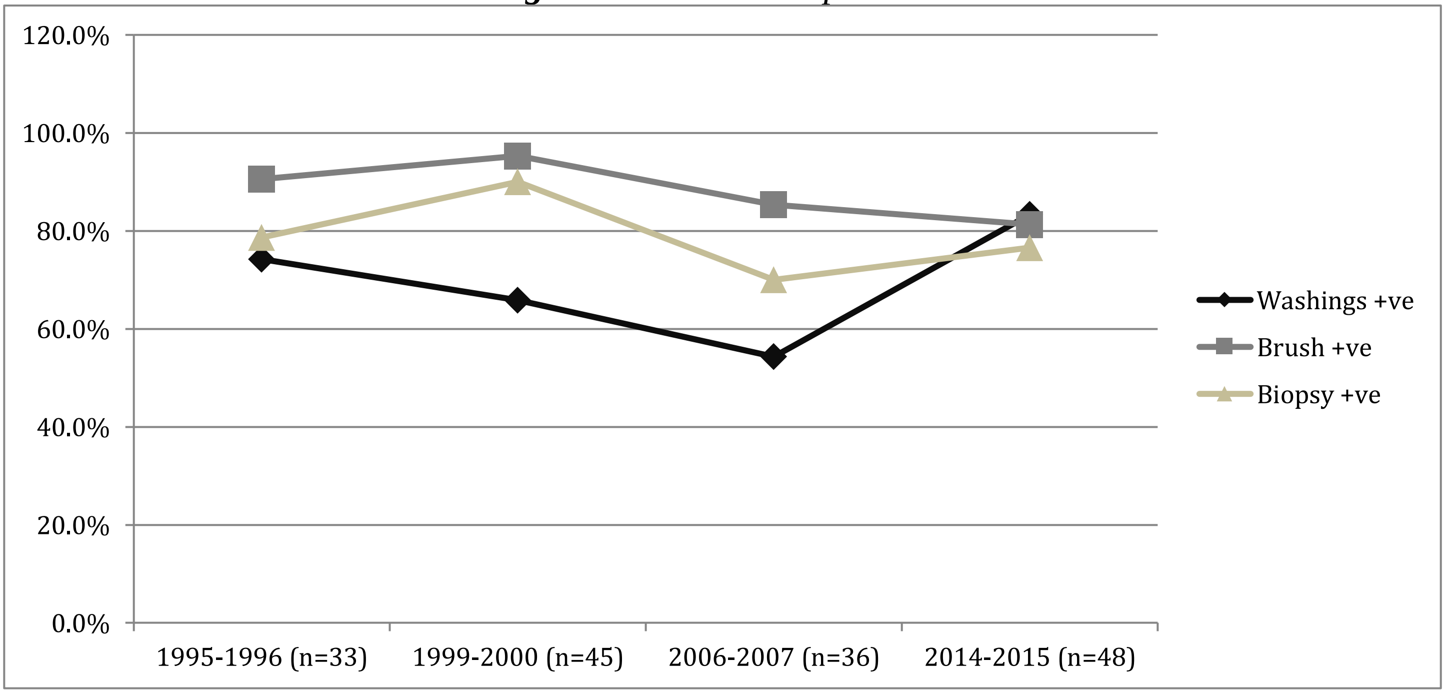


Figure 5: *Bronchoscopic Yield*



Bronchoscopy pickup rate

Although 48 patients were given a diagnosis of malignancy through bronchoscopic results, a further 11 patients had a negative bronchoscopy which was followed by a diagnosis of lung malignancy through other means. The overall bronchoscopy pick-up rate for malignancy was therefore 81.4% (48 out of 59 patients).

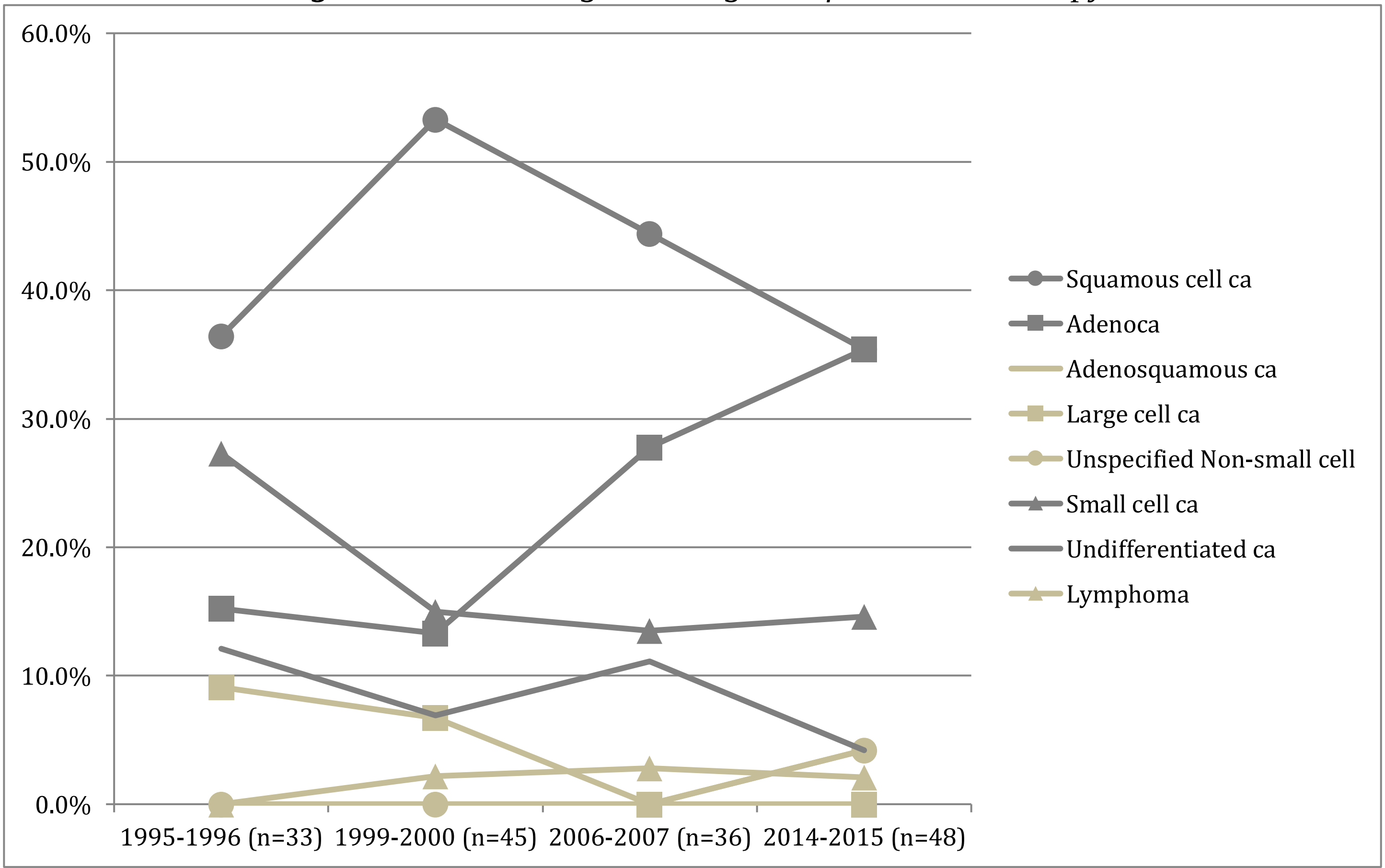
Of those patients who had a negative bronchoscopy but were eventually diagnosed with lung malignancy through alternative means, 72.7% (8 out of 11) were diagnosed with adenocarcinoma. There was one patient each for squamous cell carcinoma and small cell carcinoma, and the remaining patient had a biopsy showing necrotic cells likely originating from necrotic areas of carcinoma but no definitive diagnosis could be established. Of this same patient cohort, 72.7% (8 out of 11) presented with persistent cough, while only 9.1% (1 patient) presented with dyspnoea.

The pickup rate of bronchial washings for malignancy was 67.8% (40 out of 59 patients) and that of bronchial brushings was 67.2% (39 out of 58 patients). The pickup rate of endobronchial biopsies was 68.4% (13 out of 19 patients).

Histological subtypes

Fig. 6 shows the histological subtypes diagnosed from bronchoscopy. The prevalence of adenocarcinoma is equal to that of squamous cell carcinoma in the 2014-2015 cohort. There were no patients diagnosed with large cell carcinoma in the 2014-2015 group. Immunohistochemistry results were available for 21 patients (33.9%).

***Figure 6**: Final Malignant Diagnosis from Bronchoscopy*



In the male cohort, adenocarcinoma and squamous cell carcinoma were equally prevalent (15 patients – 37.5%). These were followed by small cell carcinoma (14.6% or 7 patients). There were no males diagnosed with adenosquamous carcinoma. The lymphoma and undifferentiated carcinoma patients were all male, and one of the patients with unspecified non-small cell carcinoma was male.

The female cohort showed an equal distribution between adenocarcinoma, squamous cell carcinoma and adenosquamous carcinoma, each accounting for 25% (2 patients). 1 patient had small cell carcinoma, and the remaining patient was diagnosed with unspecified non-small cell carcinoma.

Of those 6 patients presenting with brain metastasis who had a positive bronchoscopy, 3 patients were diagnosed with adenocarcinoma, 2 patients with squamous cell carcinoma and the remaining patient was diagnosed with unspecified non-small cell carcinoma.

Discussion

Molecular profiling studies serve to remind us that lung cancer is a complex disease, with different phenotypes that are characterized by variation in morphology as well as molecular composition. Over recent decades, there appears to be worldwide shifts in the relative frequencies of various phenotypic patterns of lung cancer, which are even more striking than changes in the overall incidence of lung cancer.[3]

When comparing presenting symptoms of lung malignancy over the years, it is noticeable that in our local cohort of patients, cough (41.7% of patients with a positive bronchoscopy) and dyspnoea (35.4%) have become more common, possibly explained by the fact that medical practitioners are investigating these symptoms more thoroughly. Cough was even more common among malignancy patients with a negative bronchoscopy (72.7%); these patients most likely had peripheral tumours, and the cough suggests involvement of peripheral nerves. In contrast, patients with a positive bronchoscopy were more likely to present with dyspnoea (35.4%) than those with a negative bronchoscopy who were diagnosed with malignancy through other means (9.1%). This is probably because patients with a positive bronchoscopy had central lesions which compromise more lung function.

Unfortunately, a larger number of patients presented with brain metastasis when compared to the previous 15 years. The incidence in our local cohort (12.5%) is similar to that quoted in a study performed by Shouten *et al*.[4] (16.3%). All cases of brain metastases occurred in conjunction with non-small cell lung cancer. Although small cell lung cancer classically carries a high risk of brain metastases, non-small cell lung cancer is also commonly associated with brain metastases and the risk can be as high as 23.2%.[5] The absence of small cell lung cancer patients with brain metastases is probably due to the fact that small cell lung cancer was diagnosed in only a small percentage of our cohort (14.6%).

Previous local data identified a persistent decrease in the male:female ratio for lung malignancy, reflecting international trends. This trend was not reflected in our study, and the significance of the drop in females is unclear. International studies have also shown an increase in lung cancer in never-smokers, and the reasons for this remain uncertain.[6] Our local data show a small decline in the percentage of male lung malignancy patients with a positive smoking history over recent years, while there is no consistent trend in the female smoking history, with females having a positive smoking history varying from 16 to 67% over the last two decades.

When comparing diagnostic methods performed during bronchoscopy, a significant improvement in the lavage is noticeable. However, these results were not mirrored in the results obtained from the bronchial brushings. A plausible explanation could be the introduction of different branded bronchial brushes in our hospital, with the resulting technical difficulties associated with them. Results of endobronchial biopsies have given similar yields possibly due to that fact that more experienced staff tend to perform such a procedure, while brushings are usually carried out by respiratory trainees performing the bronchoscopy under supervision.

The bronchoscopy pick-up rate for malignancy of 81.4% was calculated by following up those patients who had a negative bronchoscopy but were diagnosed with lung malignancy through alternative means. The previous local study by Agius *et al.* did not follow up patients in this manner, and therefore do not quote any pick-up rates. Our results show that most lung cancer patients who had a negative bronchoscopy were diagnosed with adenocarcinoma (72.7%), and this is probably because adenocarcinoma tends to be peripheral and therefore less amenable to bronchoscopic techniques.

Previous results have shown that squamous cell carcinoma was the most frequent histological subtype; however, our recent study has shown that adenocarcinoma and squamous cell carcinoma are equally diagnosed. Histology trends show a persistent upward trend in the adenocarcinoma histological subtype in both males (37.5% in our cohort vs 31% in the 2006-2007 cohort) and females (25% vs 14.3%), and a decline in the squamous cell carcinoma subtype in both gender groups (males 37.5% vs 44.8%; females 25% vs 42.9%). International studies have also identified similar trends with a significant increase in the incidence rate of adenocarcinoma and drop in the rate of squamous cell carcinoma.[2,7-11] The increasing proportion of lung cancers classified as adenocarcinoma has been a topic of interest and research for a number of years. To date, the cause of the increase in adenocarcinomas is not clear. Two changes in cigarette design over time have been proposed to explain the rise of adenocarcinoma in females. First, ventilated filters, which have gained popularity over the last several decades, have led to compensatory smoking, where smokers inhale a greater volume of smoke more deeply, leading to increased exposure of cells on the periphery of the lung (where adenocarcinoma occurs) to carcinogens. Secondly, filtered cigarettes are richer in nitrate, increasing the exposure to N-nitrosamines, which are associated with an increased risk for adenocarcinoma but not with other types of lung cancer.[7]

A similar number of bronchoscopies has been performed during the study period compared to the previous study, despite the increasing number of CT-guided lung biopsies performed in our hospital. This implies that there is a probable overall increase in the incidence of lung malignancy locally. In our study, we also looked at patients who had suspected malignancy whose eventual malignant diagnosis was made from CT-guided biopsy following a negative bronchoscopy, whereas in the previous study, such patients were not taken into consideration, possibly due to the fact that there were no patients who had a CT-guided biopsy performed following a normal bronchoscopy, since the procedure was not available at the time.

Limitations of the Study

Patients who never had a bronchoscopy but were diagnosed with lung malignancy through radiologically-assisted biopsy or other means, were not included in the study. This implies that the results of the study may not be totally representative of the lung malignancy trends in Malta. Only the results of one of four respiratory consultants' bronchoscopies were analysed. Since bronchoscopy results tend to depend on the operator performing the procedure, one respiratory firm was chosen in order to standardize the bronchoscopy procedure as much as possible.

Conclusion

Adenocarcinoma has increased in both males and females separately in Malta, and now has a similar prevalence to squamous cell carcinoma. On a positive note, several genetic mutations specific to lung adenocarcinomas have been found, representing attractive targets for molecular therapy.

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Original Article

Rituximab – A Novel Treatment for Pemphigus in Malta

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Abstract

Until recently, the main treatment for pemphigus has been systemic corticosteroids, usually administered at high doses with consequent side-effects. Lately, the biological agent rituximab has been introduced as an effective treatment for this condition.

This article describes seven cases of pemphigus successfully treated with rituximab in Malta and discusses the benefits and drawbacks of this novel treatment modality.

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Key words

Pemphigus Vulgaris; Rituximab; Immunomodulation

Introduction

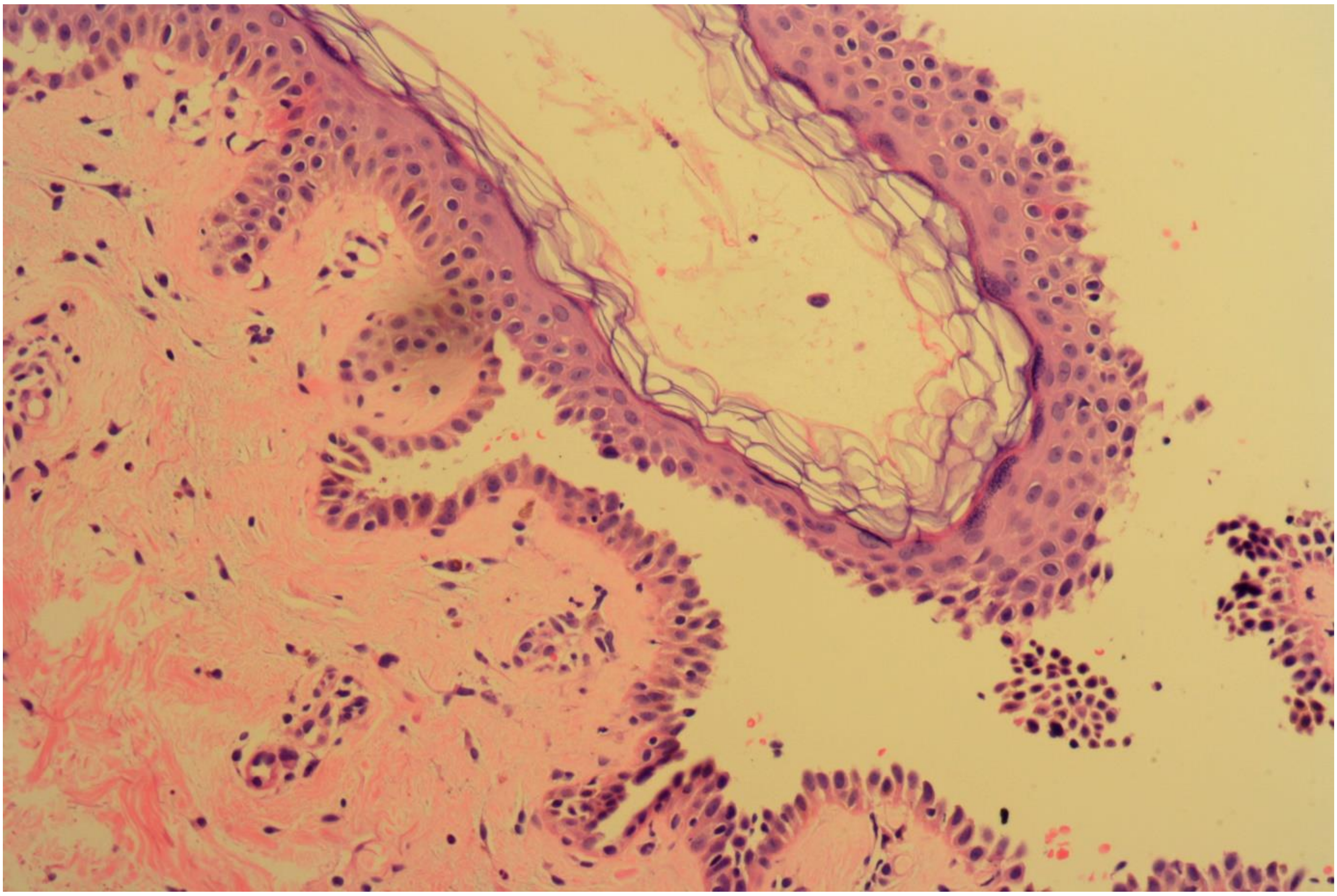
Pemphigus is an uncommon but serious cutaneous immunobullous disorder, generally of the middle-aged, where blistering occurs intraepithelially, at the level of the intercellular desmosomes due to autoantibodies (typically to desmoglein 3 in mucosal-dominant disease and to desmoglein 1 and desmoglein 3 in mucocutaneous disease).[1-2] The pathogenic role of anti-desmoglein autoantibodies is evidenced by development of pemphigus vulgaris-like lesions in neonatal mice infused with anti-desmoglein IgG and occurrence of a pemphigus vulgaris-like syndrome in genetically-modified desmoglein 3 knockout mice.[3]

In pemphigus vulgaris, blistering may appear in both the skin and mucosae. Skin blisters and erosions occur in the majority of cases at some stage, mostly on the scalp, face, neck, back and upper chest.[4] Mucosal disease is the only manifestation in some cases. Apart from being life-threatening, pemphigus has a major impact on patients' quality of life, causing significant pain and discomfort, especially in cases with oral involvement.

Before the advent of corticosteroids, pemphigus mortality reached 75% with many patients dying of sepsis, *Staphylococcus aureus* being the commonest pathogen on diseased skin.[5-6] Until recently, the mainstay of therapy has been systemic steroids combined with steroid-sparing agents such as azathioprine,[7] mycophenolate sodium[8] and cyclophosphamide.[9] Other treatments employed with variable efficacy include cyclosporine,[10] intravenous immunoglobulins,[11] photodynamic therapy,[12] immunoadsorption[13] and plasmapheresis.[14] There are no large randomised controlled trials comparing different treatment regimens so data is limited to that derived from retrospective studies.[8] Modern pemphigus treatment has decreased mortality to under 5%, however, the need for steroids to control disease in most cases exposes patients to significant side-effects.[9]

Rituximab is an IgG1 chimeric mouse/human anti CD-20 antibody that causes antibody-mediated B–cell lysis.[15] It has recently been shown to be effective for treating pemphigus and appears particularly useful in patients in whom traditional therapy is insufficient or inappropriate.[16] The drug has become available locally and this article describes its use in seven cases of pemphigus vulgaris in Maltese patients.

Figure 1: *H&E x40 - Histology of skin biopsy of Case 1 showing the split just above the basal layer, with tombstone morphology of the remaining basal cells and acantholytic cells in the blister lumen*



Case series

We report seven cases of pemphigus vulgaris treated with rituximab in Malta between 2013 and 2016. Four patients were male and three were female with a mean age at diagnosis of 57 years (range 44-70 years). The main presenting features were blisters, superficial ulcers and erosions on the trunk and head and neck. Five patients had painful ulcers and erosions in the oral mucosa. Other symptoms reported included hoarseness, odynophagia, nosebleeds, auditory canal erosions and crusted plaques on the trunk.

All cases were confirmed histologically, with intraepidermal clefting and acantholysis seen in all cases. Direct immunofluorescence was available in five cases, all of which showed typical intercellular C3 and IgG deposition in the epidermis. The histology of one of our patients is shown in Figure 1.

Various systemic treatments were given before administration of rituximab. These included oral and intravenous steroids, azathioprine, mycophenolate sodium, methotrexate, dapsone, intravenous immunoglobulins and colchicine.

The rituximab regimens used in our patients were once-weekly 500mg intravenous infusions for four weeks or two intravenous infusions of 1g two weeks apart. Excellent responses were reported in all cases after a few weeks. Three patients entered remission after only one rituximab cycle. Four patients had recurrences after an average of six months but the symptoms were milder in all cases. Of these patients, two went into remission after the second cycle of rituximab whilst another patient went into remission after the third cycle of rituximab. One patient had a very mild recurrence which was treated successfully with intravenous immunoglobulin. Some low-dose immunosuppressive treatment continues to be required to maintain control in all patients. This includes mycophenolate combined with low-dose prednisolone (5mg daily), azathioprine in isolation, and azathioprine combined with low-dose prednisolone (5mg daily). Improvement of cutaneous features following rituximab in one of our patients is shown in Figure 2.

***Figure 2**: Case 5 before (left) and after (right) rituximab therapy, showing resolution of extensive blistering and erosions on the back*

Table 1: Details of 7 cases of pemphigus vulgaris treated in Malta with rituximab between 2013 and 2016 (IVIG – intravenous immunoglobulins)

	Age at diagnosis (years)	Sex	Symptoms at presentation	Histology & Immunofluorescence (IF)	Treatment attempted before rituximab	Rituximab regimen/doses used	Response	Rituximab side-effects
Case 1	51	F	• Painful ulcers on hard palate and buccal mucosa • Nose bleeds • Persistent sore throat • Auditory canal erosions	• Suprabasal blistering with acantholytic cells in intraluminal bulla • Dilapidated brick wall appearance • IF – weak intercellular positive staining in basal layers for C3 and IgG	• Prednisolone + azathioprine • Prednisolone + iv methylprednisolone + mycophenolate sodium	- 4 once-weekly 500mg infusions - 1 g 2 weeks apart for 2 subsequent infusions	After 1st – dramatic improvement + minor recurrence after 6 months After 2nd – slight recurrence after 1 year After 3rd - remission	Minor reaction during 3rd cycle - pruritic erythema on the hands, spreading to arms and face; no systemic symptoms
Case 2	53	M	• Odynophagia • Mouth ulcers • Hoarseness • Blisters on left supraclavicular area and chest	• Intraepidermal clefting with acantholysis • Basal keratinocytes still attached to basement membrane with a tombstone appearance • Sparse chronic inflammatory cell infiltrate including a few eosinophils • IF – intercellular C3 and IgG deposition in epidermis	• Prednisolone • Prednisolone + azathioprine	- 4 once-weekly 500mg infusions, - 1 g 2 weeks apart for 1 subsequent infusion	After 1st –improvement + minor recurrence after a few weeks After 2nd – remission	Nil
Case 3	44	M	• Blisters over scalp, chest and abdomen	• Suprabasal acantholysis • IF - intercellular C3 anf IgG deposition in epidermis	• Dapsone • Dapsone + prednisolone • IVIG	- 4 once-weekly 500mg infusions - 2 500mg infusions	After 1st – improvement + flare after 9 months After 2nd – remission	Nil

Case 4	50	F	• Extensive painful oral ulcers	• Suprabasal acantholysis with basal keratinocytes remaining intact with a tombstone appearance • Superimposed viral changes within nuclei of keratinocytes implying superimposed herpes simplex • IF – IgG deposition in epithelium	• Prednisolone + azathioprine	- 4 once-weekly 500mg infusions	Remission	Nil
Case 5	63	M	• Scaly eruption over chest • Plaques on face, scalp, neck and upper trunk, limbs and thighs • Erosions in oral mucosae • Blisters on lower back	• Intraepidermal blister with partially preserved basal keratinocytes • Mild chronic inflamation with a few eosinophils • IF - equivocal IgG and C3 deposition intercellularly in the epidermis	• Topical clobetasone • Prednisolone • Azathioprine	- 1g 2 weeks apart	Recurrence with facial bullae, for which he was given IVIG, then entered remission	Nil
Case 6	69	F	• Mouth ulcers • Blisters on lower back	• Mucosal hyperplasia + suprabasilar clefting • Acantholysis • Basal keratinocytes with a tombstone appearance • IF – Not available	• Prednisolone + azathioprine	- 1g 2 weeks apart	Remission	Nil
Case 7	70	M	• Persistent lip ulcer • Blister over scar	• Submucosal epithelial split with hobnail type mucosal cells • Underlying haemorrhage • IF – Not available	• Prednisolone • Prednisolone + azathioprine • Prednisolone + colchicine • Prednisolone + IVIG • Prednisolone + IVIG + dapsone • IVIG + Dapsone	- 1g 2 weeks apart	Remission	Nil

Rituximab was well tolerated in all cases with only one patient developing a significant side-effect, namely pruritic erythema on the hands spreading to the arms and face without systemic symptoms during the third treatment cycle. The infusion was stopped and the erythema resolved without treatment within two hours.

Details of the seven cases are shown in Table 1.

Discussion

The mechanism of rituximab action is not yet fully-understood. Although it decreases production of pathogenic auto-antibodies, it does not affect levels of protective antibodies and so total antibody titre remains unchanged. One theory for this is that whereas pathogenic autoantibody-producing plasma cells are CD-20 positive and thus targeted by rituximab, protective plasma cells are CD-20 negative and hence not targeted.[17]

Rituximab entered clinical use in the 1990s, mainly to treat lymphoma and rheumatoid arthritis. Other indications include ANCA-positive vasculitis, systemic lupus erythematosus, dermatomyositis and primary Sjogren's syndrome.[15] It was first used in the context of autoimmune bullous diseases in 1999 by Heizmann et al who reported a case of paraneoplastic pemphigus successfully treated by rituximab, and is increasingly being used worldwide in the management of pemphigus.[18] Locally it was first used to treat pemphigus in 2013. Other autoimmune bullous diseases for which treatment with rituximab has been employed include bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita.[19]

Rituximab has a half-life of around 20 days, and is given by slow intravenous infusion.[15] The dosing protocols most commonly used are the lymphoma protocol, consisting of four weekly infusions of 375 mg/m^2 and the rheumatoid arthritis protocol, where two infusions of 1g are given two weeks apart.[2] However, there is no scientific rationale reported in the literature as to why these two protocols should be used in pemphigus. The protocols appear equivalent in terms of remission and relapse rates although remission may be more prolonged with higher rituximab doses.[20] Rituximab may be administered in conjunction with intravenous immunoglobulins, with early studies of such combination treatment reporting promising results.[16,21]

Infusion reactions have been reported in 25% of individuals receiving their first rituximab dose. Such reactions tend to be mild to moderate in nature, the severity decreasing with subsequent doses. The risk of infusion reactions may be reduced by premedication (including analgesics, antihistamines and steroids).[15] In our series, a minor cutaneous infusion reaction occurred in one patient, during her eighth infusion, despite premedication with prednisolone, chloremphenamine and paracetamol. Other more serious possible adverse events include an increased infection risk (including opportunistic pathogens), progressive multifocal leukoencephalopathy, cytopenia and cardiac events in individuals with underlying cardiac problems. The incidence of severe adverse effects does not appear to be influenced by the protocol used.[20] Paradoxical worsening of pemphigus following rituximab infusion has also been reported.[22]

Contraindications to rituximab include severe immunosuppression, active infection, uncontrolled cardiac disease and recent live vaccination. Before starting rituximab, patients should be screened for cardiac disease, current or previous infections that could be reactivated (e.g. tuberculosis and viral hepatitis) and vaccination status (especially for pneumococcal disease and influenza) checked. Viral hepatitis is not an absolute contraindication, however, it must be looked out for, and a decision on whether or not rituximab may be prescribed taken in the light of expert hepatological advice.[15] Due to its reported adverse effects on pregnancy, women are advised to avoid pregnancy during treatment and for at least 12 months afterwards.[15,23]

Patients treated with rituximab should be monitored for signs of infection and neurological complications. Basic blood tests, including full blood count, renal profile and liver enzyme levels should be assessed regularly. It is also recommended that serum immunoglobulins and lymphocyte subsets are checked prior to each subsequent dose.[15]

Despite not being a new drug per se, specific long-term complications, if any, of rituximab use in pemphigus, have yet to be described. Currently, dermatologists are using the drug in patients unresponsive to conventional therapy or in patients in whom conventional therapy is contraindicated because of adverse effects.[16] It may also be used as a first-line treatment, although the exact place of rituximab in the routine management of pemphigus has yet to be determined.[2] Undoubtedly a major drawback of the drug is its cost, which, like other biological agents, is much higher than that of conventional treatment. In fact, the current drug cost of four 500mg doses of rituximab is estimated to be €5710.00 (€1427.50 x4) *(Mr. Joe Sciberras, Senior Pharmacist, Sir Paul Boffa Hospital, personal communication)*.

Apart from controlling relapses of pemphigus,[21] rituximab may also produce long-term disease remission. A study in India on 25 patients (21 with pemphigus vulgaris and four with pemphigus foliaceus) reported a complete remission rate of 88% following rituximab, complete remission defined as absence of lesions for two months. Furthermore, this study reported a decrease in the cumulative corticosteroid dose of 69.6% when compared to patients treated with prednisolone alone.[2] Another study[20] reported complete remission rates of 76%, with a mean time of 5.8 months to remission and a mean duration of 14.5 months of remission; relapse rates were reported to be 40%. However, it is important to consider original disease severity when interpreting such statistics. In our cases rituximab clearly had a major suppressive effect on disease activity. It was well tolerated apart from a minor cutaneous reaction in one patient.

Conclusion

The results of rituximab therapy of pemphigus are promising. The drug appears to be generally well tolerated and may produce long-term remission, reducing the need for systemic steroids in affected patients. Further experience should help define the place of rituximab in the management of pemphigus.

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Original Article

Recreational drug use and the emerging challenges of psychoactive substances in Malta – A case series

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Abstract

Introduction: Recreational drug-related hospital admissions, excluding alcohol, appeared to be relatively constant in Mater Dei Hospital (MDH), Malta's sole public, acute general hospital. While 'classical' recreational drugs such as cocaine, heroin and Methylenedioxymethamphetamine (MDMA) were always seen as the main culprits, intoxications secondary to novel psychoactive substances (NPS) have recently emerged in MDH. The aim of this study was to determine the challenges of acute recreational drug intoxication, including NPS, in MDH.

Methods: All MDH admissions secondary to acute recreational drug intoxication between 2010 and 2015 were investigated. MDH clinical performance unit (CPU), hospital data files, hospital discharge letters and the hospital database software system were utilised for data collection. Intoxications associated with deliberate self-harm, mechanical injury and lone alcohol ingestions were excluded.

Results: 286 patients were admitted to MDH with recreational drug intoxication between 2010-2015, with a peak of 71 patients in 2015. 78.3% were males and the median age was 26 years. While 79% of the admissions were Maltese nationals, there was a surge in foreigner admissions, from 11.8% between 2010-2012 to 28.3% between 2013-2015 ($p<0.001$). Admissions occurred mostly in spring and summer, on Saturday or Sunday, and at night. 52.4% of admissions were acutely confused. Ethanol co-ingestion (40.9%) and polydrug use (39.9%) were common in these admissions. 16% needed admission to critical care. 91.3% admissions were secondary to 'Classical' recreational drugs, mostly heroin and cocaine. In 2015, 36.6% of admissions were secondary to NPS, mostly synthetic cannabinoids (SCRA). SCRA admissions were associated with severe sympathomimetic and neuropsychiatric features. An SCRA toxidrome mnemonic (MEET_SCRA) is proposed from the most common features of lone intoxications.

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Conclusion: Recreational drugs were associated with significant hospital burden, with NPS representing a new threat to MDH and Maltese public health. The toxidrome mnemonic MEET_SCRA could potentially aid in the identification of SCRA intoxications.

Keywords

Novel Psychoactive substances, NPS, Recreational drugs, SCRA, Meet_SCRA

Introduction

Recreational drug intoxications, excluding alcohol, presenting to the Emergency department (ED) in Europe is a common problem resulting in between 0.3% to 0.45% of their ED attendances in studies by Dines et al.[1] and Liakoni et al.[2]

Similar ED data from the Unites States (US) shows a worse picture, with about 2.5 million patients or 2% of the total ED visits resulting from drug abuse or misuse in 2011, of which 51% were attributable to illicit drug use.[3] Apart from the classical psychoactive substances, NPS, often known as 'Legal Highs', started to appear worldwide in the mid-2000s, specifically designed to evade drug laws with the potential of causing grave threats to public safety.[4] Recent studies from European and US ED's showed an increase in reported NPS intoxications, with resulting increased challenges for these already strained departments.[1,3,5]

Malta is the smallest country member of the European Union, with a population of around 425,000 in 2013[6] and is a major tourist destination with around 1.6 million tourists every year, including many young adults.[7]

MDH has an inpatient bed capacity of 949 beds, including 20 intensive care beds, with the ED seeing an average of 110,000 patients per year.[8] A total of 27,158 patients were admitted through the ED in 2012.[9] Throughout the years, recreational drug-related admissions to MDH appeared to be relatively constant with cocaine, heroin and MDMA being the main culprits, especially in the summer period. This correlates well with studies showing increased prevalence of recreational drug use in places of recreation.[10-11]

The aim was to describe the trends and impact of recreational drugs between 2010 and 2015 on MDH, and the impact of novel psychoactive substances in the local scene. Finally, this audit will attempt to describe the toxidrome for SCRA toxicity that will hopefully aid future professionals dealing with such NPS poisonings.

Method

All the patients admitted to MDH with acute recreational drug intoxication in the 6-year period (1st January 2010 to the 31st December 2015) were included in this retrospective study.

For the aims of this study, only patients admitted to hospital secondary to acute intoxication from a drug taken for recreational purposes 'to get a high' were included. Thus, patients with deliberate self-harm or when it was not clear whether the admissions were directly related to drug intoxication (e.g. mechanical injury or withdrawal), were excluded.

Patients admitted to hospital with lone alcohol intoxication were excluded. Patients admitted to hospital following misuse of pharmaceuticals were included only if it was deemed that these drugs were used for recreational purposes. Recreational drugs were deemed to have been involved if the patient self-reported their use, or if these were later found in drug toxicology tests, one not excluding the other. In cases where patients abused of a recreational drug while on a prescribed medication/s, the prescribed medication/s were added to the study only if the patient self-reported its use as a recreational drug, or if drug toxicology tests tested positive for a psychotropic drug that was not their routine medication on admission. The patients admitted after intoxication from a self-reported use of a lone SCRA, were further investigated by gathering data on their baseline parameters and clinical features in an attempt to describe a SCRA toxidrome. Information was gathered through the hospital CPU data, using a clinical coding system based on discharge letters. Data was also gathered through the patient discharge notes (through an electronic case summary software database), through patient medical records, and through the use of a hospital database software system (I-Soft Clinical Manager®).

Statistical Analysis

Continuous variables were presented as mean (standard deviation) and median (interquartile range) for non-Gaussian variables and were compared by the Mann-Whitney *U* test. Pearson's chi-square test or Fisher's exact test (where appropriate) were performed to compare multiple categorical variables, presented as number (percentage) for the time period 2010 to 2015. Since the overall numbers were small, these were also grouped in two time periods (2010-2012 and 2013-2015) so as to increase statistical significance. Data analyses was carried out via Excel® 2011 and SPSS-software, version 19.0. Armonk, NY: IBM Corp. A p-value <0.05 was considered statistically significant.

Results

Admissions to MDH (2010-2015)

In total, 286 patients were admitted to MDH with acute recreational drug intoxication in the 6-year period between 1st January 2010 and 31st December 2015. The average number of admissions in this period was 47.7, with a peak of 71 admissions in 2015.

Patient Demographics

Male patients constituted 224 (78.3%) of the admissions between 2010 and 2015. There was no statistically significant difference across the genders during the 6-year period (Table 2). The mean (SD) age between 2010 and 2015 was 28.3 (9.68) years, while the median age (IQR, range) was 26 (20-34, 13-60) years. The median (IQR, range) age for males was 27.5 (22-35, 14-60) years while that for females was 22 (18.3-31.8, 13-50) years (p=0.002). 226 (79%) of all admissions to MDH between 2010 and 2015 were Maltese nationals. Foreigner admissions increased from 11.8% between 2010-2012 to 28.3% between 2013-2015 (p<0.001) (Table 2).

Spring and summer (Table 2) were the most common seasons for admissions, while the fewest presentations occurred in February (Fig.1).

Saturday (50, 17.5%) and Sunday (61, 21.3%) were the most common days of presentation, with Tuesday being the least common date of admission (30, 10.5%) (Fig. 2).

136 or 47.6% of presentations occurred during the weekend (Friday 17:00hrs-Monday 07.59hrs). There was no statistically significant difference in this trend between 2010-2015 (Table 2). 145 or 50.7% were night presentations (20:00hrs-07.59hrs). There was a statistically significant increase in night presentations in the latter years (2013-2015) as compared to the earlier years (2010-2012) (p=0.017) (Table 2).

Table 1: *The number of admissions secondary to the most common recreational drugs compared across the earlier (2010-2012) and latter (2013-2015) years.*

The most common recreational drugs	Number of admissions involving recreational drug N, percentage of admissions 2010-2015 (%)	2010-2012	2013-2015	P-value
	N (%)	N (%)	N (%)	
Heroin	126 (44.1)	62 (48.8)	64 (40.3)	0.147#
Cocaine	119 (41.6)	48 (37.8)	71 (44.7)	0.242#
MDMA/ methamphetamine /amphetamine	63 (22)	38 (29.9)	25 (15.7)	0.004#
Cannabis	54 (18.5)	24 (18.9)	29 (18.2)	0.887#
SCRA	**26 (9.1)**	**0 (0)**	**26 (16.4)**	**<0.0001***
Benzodiazepines	25 (8.7)	11 (8.7)	14 (8.8)	0.966#
Synthetic Cathinones	**11 (3.8)**	**9 (7.1)**	**2 (1.3)**	**0.013***

Statistical tests used - #: Pearson's chi square test, *: Fisher's exact test used

Figure 1: *Percentage admission per month (2010-2015)*

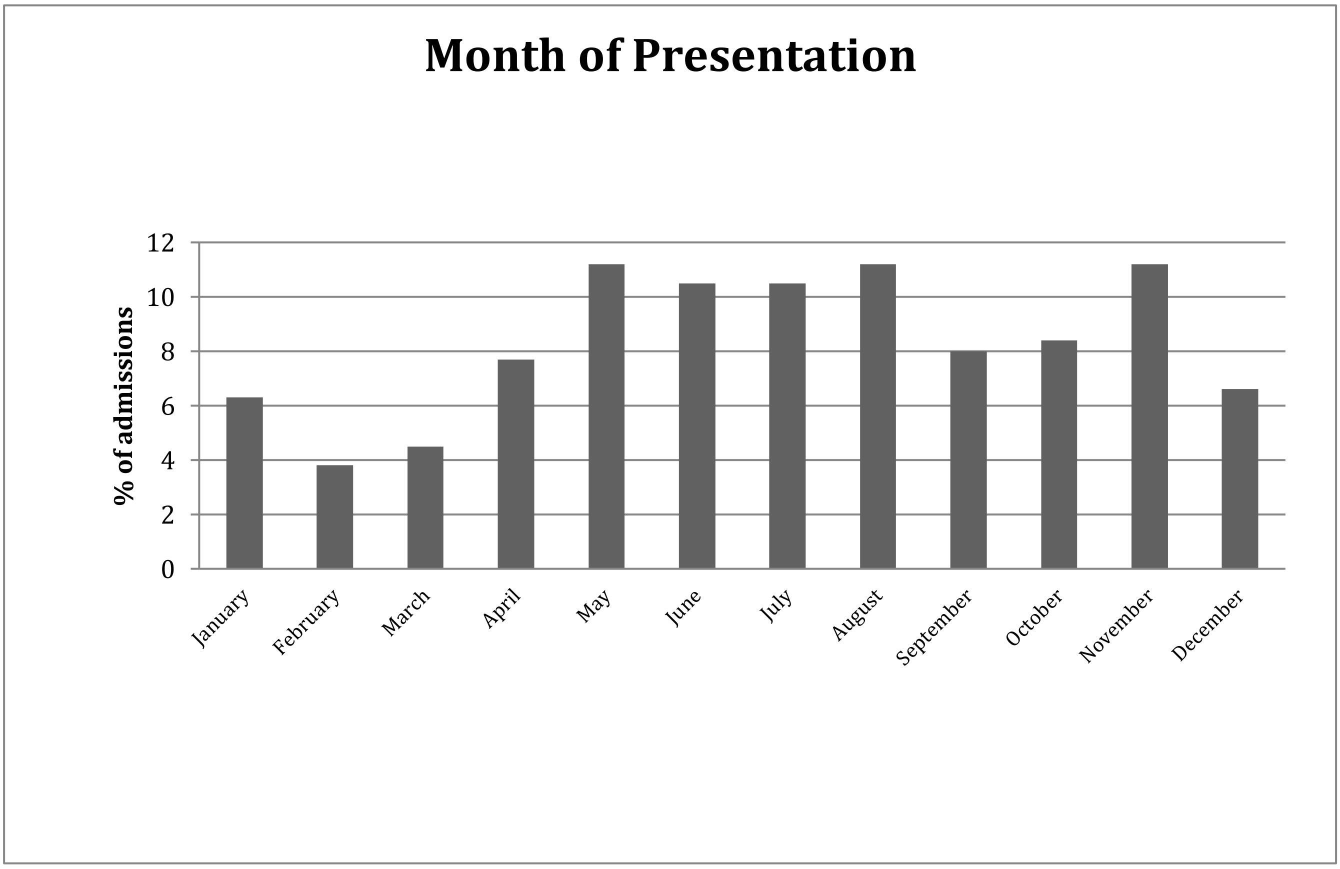


***Table 2:** Multiple categorical variables with their respective p-value between 2010-2015 and for the grouped years 2010-2012 and 2013-2015.*

		2010	2011	2012	2013	2014	2015	P-value	2010-2012	2013-2015	P-value
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	
Gender	Male	31 (79.5)	44 (88)	30 (78.9)	32 (84.2)	39 (78)	48 (67.6)	**0.136$**	105 (82.7)	119 (74.8)	**0.11$**
	Female	8 (20.5)	6 (12)	8 (21.1)	6 (15.8)	11 (22)	23 (32.4)		22 (17.3)	40 (25.2)	
Nationality	Maltese	37 (94.9)	46 (92)	29 (76.3)	31 (81.6)	36 (72)	47 (66.2)	**0.001***	112 (88.2)	114 (71.7)	**0.001$**
	Foreign	2 (5.1)	4 (8)	9 (23.7)	7 (18.4)	14 (28)	24 (33.8)		15 (11.8)	45 (28.3)	
Ward	Normal	35 (89.7)	40 (80)	35 (92.1)	25 (65.8)	45 (90)	59 (83.1)	**0.028***	110 (86.6)	129 (81.1)	**0.261$**
	Critical care	4 (10.3)	10 (20)	3 (7.9)	13 (34.2)	5 (10)	12 (16.9)		17 (13.4)	30 (18.9)	
Weekend	No	24 (61.5)	27 (54)	23 (60.5)	15 (39.5)	21 (42)	39 (54.9)	**0.205$**	74 (58.3)	75 (47.2)	**0.074$**
	Yes	15 (38.5)	23 (46)	15 (39.5)	23 (60.5)	29 (58)	32 (45.1)		53 (41.7)	84 (52.8)	
Night	No	23 (59)	32 (64)	18 (47.4)	17 (44.7)	20 (40)	31 (43.7)	**0.118$**	73 (57.5)	68 (42.8)	**0.017$**
	Yes	16 (41)	18 (36)	20 (52.6)	21 (55.3)	30 (60)	40 (56.3)		54 (42.5)	91 (57.2)	
Season	Winter (December-February)	8 (20.5)	14 (28)	7 (18.4)	4 (10.5)	8 (16)	7 (9.9)	**0.004***	29 (22.8)	19 (11.9)	**0.006$**
	Spring (March-May)	7 (17.9)	10 (20)	3 (7.9)	11 (28.9)	7 (14)	29 (40.8)		20 (15.7)	47 (29.6)	
	Summer (June-August)	14 (35.9)	13 (26)	19 (50)	9 (23.7)	16 (32)	21 (29.6)		46 (36.2)	46 (28.9)	
	Autumn (September-November)	10 (25.6)	13 (26)	9 (23.7)	14 (36.8)	19 (38)	14 (19.7)		32 (25.2)	47 (29.6)	
Day of the Week	Monday	7 (17.9)	6 (12)	8 (21.1)	3 (7.9)	6 (12)	10 (14.1)	**<0.0001***	21 (16.5)	19 (11.9)	**0.53$**
	Tuesday	5 (12.8)	2 (4)	9 (23.7)	4 (10.5)	4 (8)	6 (8.5)		16 (12.6)	14 (8.8)	
	Wednesday	7 (17.9)	6 (12)	2 (5.3)	1 (2.6)	3 (6)	12 (16.9)		15 (11.8)	16 (10.1)	
	Thursday	6 (15.4)	10 (20)	3 (7.9)	4 (10.5)	7 (14)	12 (16.9)		19 (15)	23 (14.5)	
	Friday	2 (5.1)	6 (12)	7 (18.4)	7 (18.4)	4 (8)	6 (8.5)		15 (11.8)	17 (10.7)	
	Saturday	3 (7.7)	11 (22)	3 (7.9)	10 (26.3)	10 (20)	13 (18.3)		17 (13.4)	33 (20.8)	
	Sunday	9 (23.1)	9 (18)	6 (15.8)	9 (23.7)	16 (32)	12 (16.9)		24 (18.9)	37 (23.3)	
Ethanol	No	22 (56.4)	35 (70)	18 (47.4)	20 (52.6)	26 (52)	48 (67.6)	**0.128$**	75 (59.1)	94 (59.1)	**1$**
	Yes	17 (43.6)	15 (30)	20 (52.6)	18 (47.4)	24 (48)	23 (32.4)		52 (40.9)	65 (40.9)	
Number of agents taken	Single	23 (59)	28 (56)	21 (55.3)	22 (57.4)	36 (72)	44 (62)	**0.574$**	72 (56.7)	102 (64.2)	**0.199$**
	Multiple	16 (41)	22 (44)	17 (44.7)	16 (42.1)	14 (28)	27 (38)		55 (43.3)	57 (35.8)	

N: number; Statistical tests used - $: Pearson chi-square test; *: Fisher's exact test

Figure 2: *Percentage of admissions per day of the week (2010-2015).*

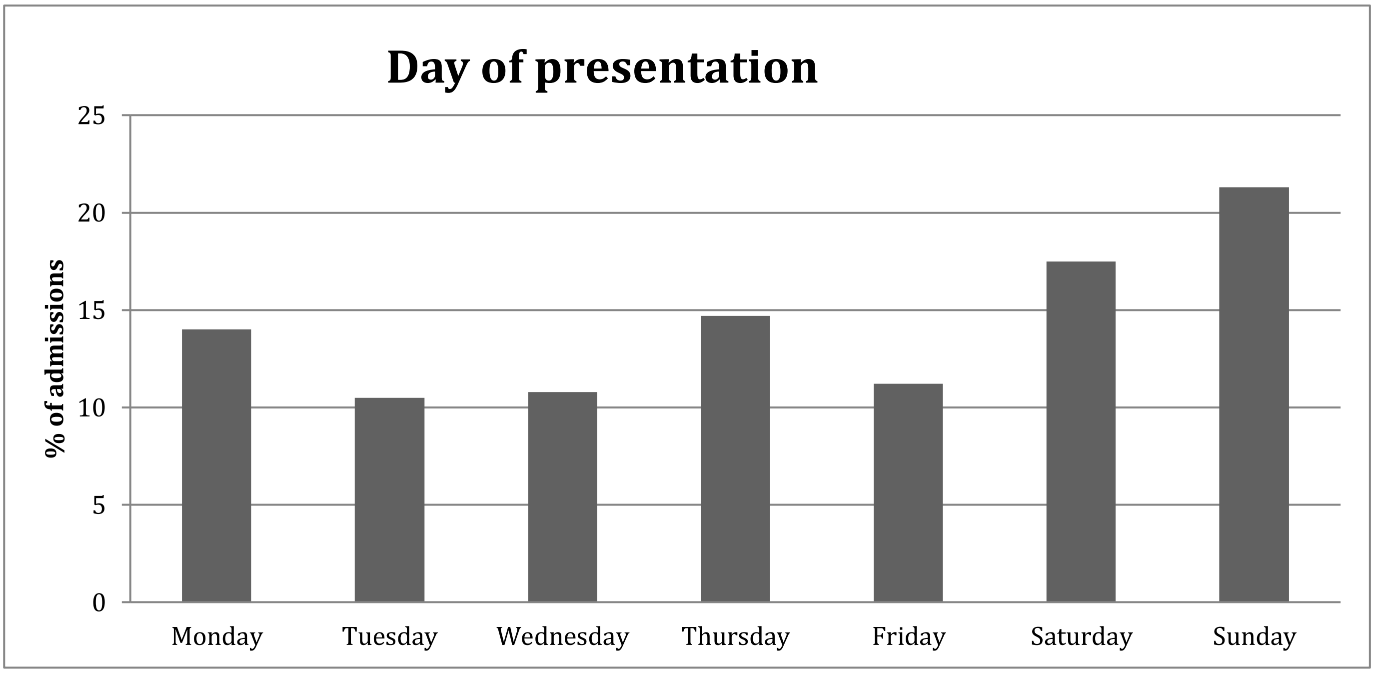


Figure 3: *Percentage of admissions per number of recreational drugs taken between 2010 and 2015*

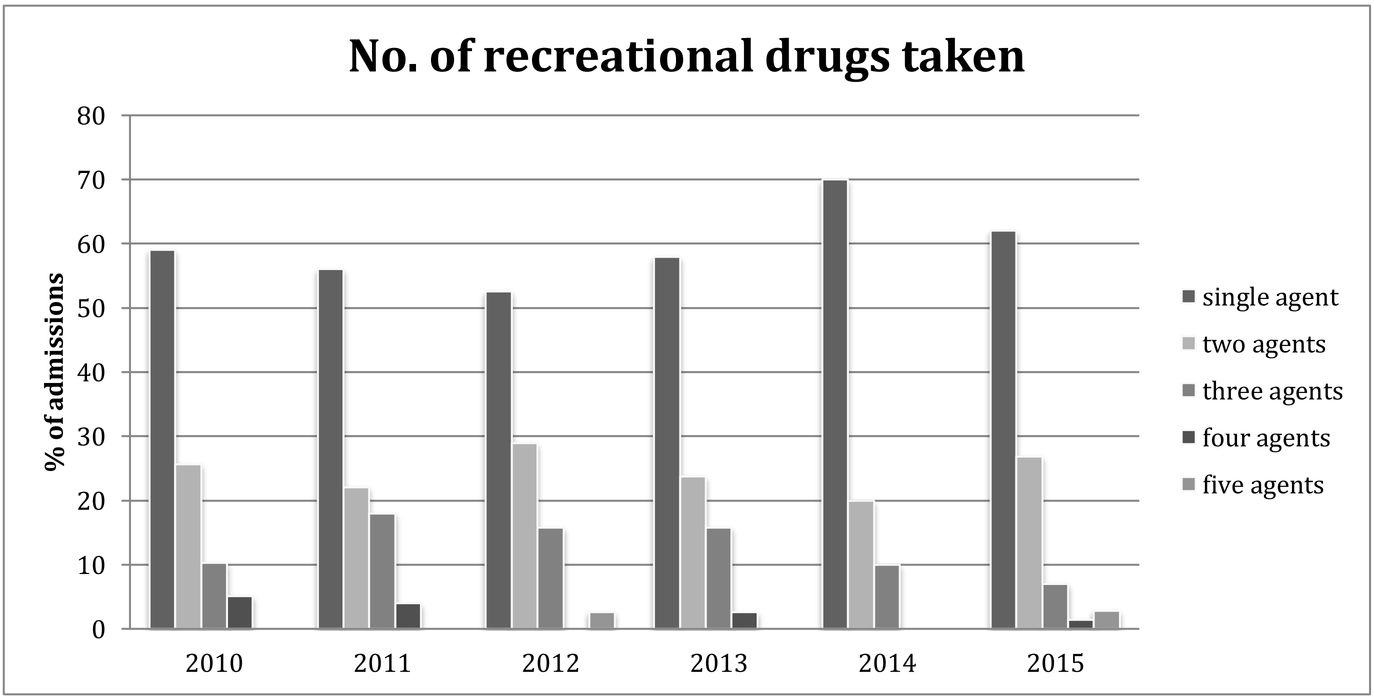
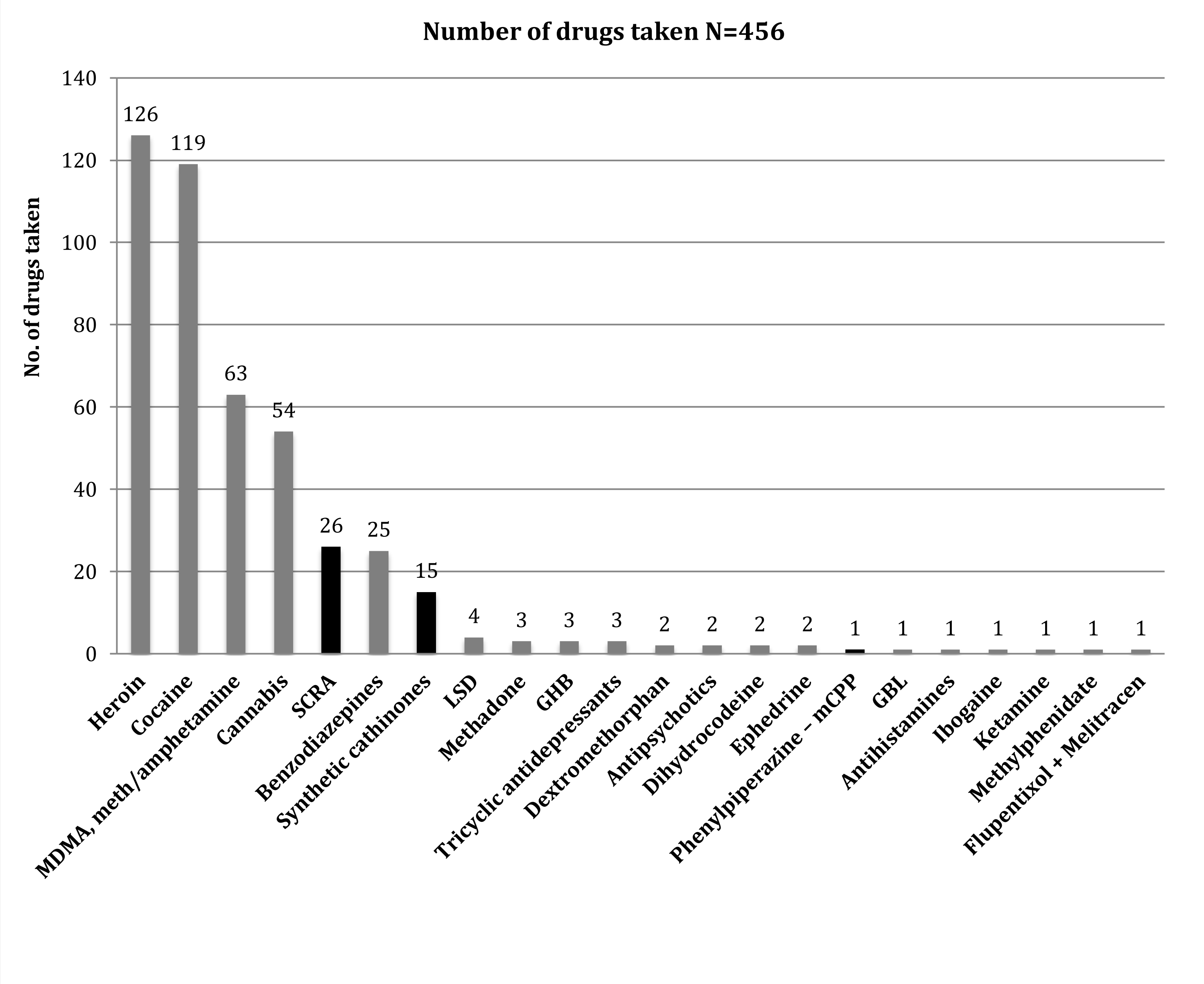


Figure 4: *All the recreational drugs taken (including NPS in black), between 2010-2015.*



Recreational drugs taken

There were 456 reported recreational drugs out of a total of 284 admissions. Ethanol was co-ingested in 40.9% of all admissions, with no significant difference across the years (Table 2). As shown in Fig. 3, a single agent was involved in most admissions (172, 60.1%), with no statistically significant change in the number of drugs taken (single or multiple) across the 6-year period (Table 2).

Of the total number of drugs taken (456), 'classical' recreational drugs were the most commonly involved with 362 (79.4%) of the total recreational drugs taken, while there were 42 (9.2%) reported NPS (SCRA, synthetic cathinones and phenylpiperazine) (Fig. 4).

'Classical' recreational drugs such as heroin, and cocaine were involved in 261 (91.3%) of the total admissions, while NPS were present in 37 (12.9%) of the admissions between 2010 and 2015. 15 of these 37 NPS admissions involved both 'Classical' recreational drugs and NPS. Of these NPS, SCRA were first reported in an

MDH admission in 2015, and resulted in 36.6% of all recreational drug admissions in that year.

43 (9.4%) pharmaceutical medications were taken in 34 admissions (11.9%) for recreational purposes. Of these benzodiazepines were the most common (26, 60.5%), with diazepam (16, 37.2%), being the commonest pharmaceutical drug.

Severity of the admissions

The average length of stay (LOS) between 2010 and 2015 was 47.2hours, while the median (IQR) LOS was 38 (23-50.9) hours. The median (IQR, range) GCS at admission to ED between 2010 and 2015 was 14 (13-15, 3-15), while the average GCS at ED was 13.2. There was no statistically significant difference in GCS between genders (p=0.239). 27 (9.44%) patients had a GCS of less than or equal to 8 on admission (comatose), while 123 (43%) had a GCS of between 9 and 14. 47 patients (16.4%) required admission to either cardiac critical care unit (CCCU) or intensive care unit (ITU).

Novel psychoactive substances

NPS were present in 37 (12.9%) admissions between 2010-2015, involving 42 (9.2%) reported NPS. 26 SCRA, 15 synthetic cathinones (MDPV, dimethcathinone, mephedrone, pentedrone, PVP and pyrovalerone) and 1 piperazine (mCPP) were involved. When NPS admissions were compared with Non-NPS admissions there was no statistical difference in terms of median GCS (p=0.297), critical bed usage (p=0.213) or median LOS (p=0.977).

Synthetic cannabinoid receptor agonists (SCRA)

Admissions secondary to self-reported SCRA intoxication were analysed in order to attempt to identify a toxidrome. In total, 18 cases were included out of a total of 26 cases of self-reported SCRA use. One medical file could not be retrieved and 6 other cases had either consumed alcohol or other drugs together with SCRA. 13 (72.2%) were males and 11 (61.1%) were foreign nationals.

MEET_SCRA

The most common features were mydriasis (66.7%), emesis (50%), euphoria (38.9%), tachycardia (77.8%), sweating (38.9%) and seizures (22.2%), confusion [GCS<15] (77.8%), respiratory depression (44.4%), respiratory acidosis (33.3%), anxiety (61.1%)/ agitation (79.9%). From these features a mnemonic for the toxidrome of SCRA intoxication is proposed (MEET_SCRA).

Discussion

Admissions with recreational drug intoxication

286 patients were admitted for recreational drug intoxication between the 1st of January 2010 and the 31st of December 2015. This represents 0.18% of the total ED admissions per year in MDH.[6] There was however a significant increase in the number of admissions in 2015 (0.26%), which would approach European figures [1, 2].

Demographics

The patients' age and gender ratios compared well with other European studies (median age of 26 years) with males amounting for more than three quarters of the MDH admissions.[1,12] 79% of the MDH recreational drug admissions were Maltese, however over the latter years there was a statistically significant increase in the number of foreigners. This was likely due to the recent increase in immigration, with Malta recording amongst the highest population growth rates in 2013.[13]

Most of these admissions attended during the night and in the summer period, while Saturday and Sunday were the most common days of admission (Table 2 and Fig. 2). This correlates well with a study by Dines et al.[1] and with the fact that some social settings like clubbing, increase the risk of recreational drug consumption.[14]

Severity of the admissions

The average LOS during this 6-year period was 47.2 hours, with a median of 38 hours. Comparison with the European study by Dines et al.[8] with a LOS of 4.6 hours (IQR 2.5-9.9 hours) was not possible, since this study included discharges from the ED.

The median GCS upon admission to the ED was 14 while the average GCS was 13.2. The fact that 27 (9.44%) patients were comatose and that 123 (43%) had a GCS of between 9 and 14 on admission, indicates the severity of such intoxications and compares well with other studies.[1-2] 47 patients (16.4%) were admitted to critical care. When comparing NPS admissions to non-NPS admissions, there was no-statistical change in terms of severity (LOS, median GCS and critical bed usage). However, note is made of the small numbers of the sample which might have affected the statistical outcome.

Recreational drugs taken

The high rate of ethanol co-ingestion (40.9%) and poly-drug use (39.9%) in these admissions relates well with other European studies.[1-2]

'Classical' recreational drugs, especially heroin and cocaine were the most common recreational drugs over the 6-year period (379, 83.1%). Pharmaceutical drugs were taken for recreational purposes in 11.9% of these admissions. In the MDH study, only 3 patients took them as a lone drug (excluding alcohol). Thus, the lone intake of a pharmaceutical drug to 'get a high' remains a very rare occurrence in MDH admissions.

Novel psychoactive substances (NPS)

NPS were present in 37 (12.9%) of all admissions and included 42 (9.2%) reported NPS. This percentage of reported NPS was twice as common in Malta than in the European study by Dines et al.[1] In 2015, 27 (24.3%) NPS were reported in 26 (36.6%) admissions, hence being significantly more than the latter study. Synthetic cathinones "bath salts" were more common in the earlier years (2010-2012), and have decreased over the latter years (2013-2015) (p=0.013) (Table 1).

The only piperazine reported, meta-Chlorophenylpiperazine (mCPP) was detected by GC/MS in 2010 and was found in a polydrug admission (together with MDMA and cocaine). The reasons for such decrease in reported synthetic cathinones and piperazines could be a change in trend use, decreased availability, or possibly the scheduling of such drugs. Mephedrone became scheduled by legal notice in Malta in 2010.[15] Also, the mass spectrometer of the GC-MS available at the MDH laboratory had not been functional for the last 6 months of 2015.

The fact that some users might be acquiring different contents, or actually different recreational drugs, to what they paid for, has also been mentioned in the literature.[16-17] This might be the reason why some patients had not self-reported the use of synthetic cathinones, even when these drugs were still not scheduled in Malta. MDPV for instance, only became scheduled in Malta in 2016.[18]

***Table 3**: Clinically reported features of SCRA intoxications*

	Total Number (N) = 18	(%)
Cardiovascular		
Tachycardia (>100bpm)	14	77.8
Bradycardia (<60bpm)	0	0
Hypotension (Systolic blood pressure<90)	1	5.6
Arrhythmias	0	0
Palpitations	2	11.1
Chest pain	1	5.6
Arrhythmias (apart from sinus tachycardia)	0	0
Respiratory		
Hyperventilation	4	22.2
Respiratory depression: pCO2 (> 45mmHg)	8	44.4
Neurological/Psychiatric		
Anxiety	11	61.1
Euphoria	7	38.9
Headache	1	5.6
Agitation/Aggressiveness	13	72.2
Psychosis	2	11.1
Hallucinations	3	16.7
Amnesia	4	22.2
Seizures	3	16.7
Twitching of muscles (myoclonus)	2	11.1
Cerebellar features	3	16.7
Pupils – Mydriasis	12	66.7
Pupils – Miosis	0	0
Pre-hospital 'Alert' on AVPU scale	7	38.9
Pre-hospital 'Not Alert' on AVPU scale i.e. V, P or U /low GCS	11	61.1
GCS on arrival to ED = 15	4	22.2
GCS on arrival to ED 9-14	13	72.2
GCS on arrival to ED < or = 8	1	5.6
Others		
Lactate >=2.0	7	38.9
Acidosis (pH <7.35)	6	33.3
Alkalosis (pH >7.45)	1	5.6
Nausea or vomiting	9	50
Respiratory acidosis only (pH <7.45, pCO2 >45mmHg, Bicarbonate > 21)	6	33.3
Metabolic acidosis only (pH <7.45, pC02 <=45mmHg, HCO3 <21)	0	0
Mixed metabolic and respiratory acidosis	2	11.1
Glucose level >9 <11.1	5	27.8
Glucose level >=11.1	2	11.1
Hyperthermia (>39degrees Celsius)	0	0
Hypothermia (<35 degrees Celsius)	3	16.7
Sweating	7	38.9
Acute kidney injury	6	33.3
Hypokalaemia (K^+ < 3.5)	5	27.8

Synthetic cannabinoid receptor agonists (SCRA)

SCRA were first reported in MDH admissions in the beginning of April 2015. From then onwards, 26 (36.6%) admissions in 2015 were from SCRA. This represented only the self-reported intoxications since there is no liquid chromatography-tandem Mass Spectroscopy (LC-MS/MS) or other analytical screen able to detect SCRA at present in Malta, and no samples were sent for testing abroad.

Sympathomimetic toxicity, respiratory complications and neuropsychiatric symptoms, were the most common reported features of lone SCRA intoxications (Table 3). This collated well with a study by Hermanns-Clausen et al.[19] involving a small sample of patients with confirmed SCRA intoxication.

Fourteen (77.8%) patients in the MDH study had documented tachycardia (range 102-145bpm). All of these patients were treated symptomatically for the tachycardia, and all had normalization of their heart rate within a few hours.

A significant number of patients had respiratory depression in this study, and this is supported by an early study on SCRA effects on animals.[20] While the study by Hermanns-Clausen et al.[19] does not mention respiratory depression or acidosis, it does emphasise the fact that a third of the patients displayed somnolence for several hours, "but still had sufficient respiration". It is reasonable to assume that respiratory depression might have been present at some point during this period of decreased consciousness. 2 case reports documenting SCRA-associated respiratory depression in two young males, both of whom required intubation, were described by Jinwala and Gupta.[21]

In the study by Hermanns-Clausen et al.[19] no patients had acute kidney injury (AKI), as defined by KDIGO[22] while this was present in 6 lone SCRA intoxications admitted to MDH. All of these admissions involved young males (16 to 36 years). Four of these 6 AKI's were hypotensive, or had documented fluid loss, such as sweating, vomiting or excessive physical activity. However, in 2 of these 6 cases neither rhabdomyolysis nor a pre-renal injury appear to fully explain the AKI, suggesting a SCRA-associated intrinsic AKI. AKI has been associated with SCRA in 16 US patients, with 6 out of 8 of such patients who had a renal biopsy, showing acute tubular injury, while 3 out of these patients showing features of acute interstitial nephritis.[23] Of these 16 patients, five required haemodialysis, most recovering within 3 days of the creatinine peak, with no reported deaths.[23] While MDH cases had normalisation of their levels within a maximum of 10 days, with none needing dialysis, two patients were discharged home before documented normalisation of their renal function.

Three patients (16.7%) in this study had generalised seizures, all of which were treated conservatively and none had status epilepticus. SCRA have been associated with seizure activity.[24]

A toxidrome mnemonic "MEET_SCRA" is proposed from the results of this study, as an aid in diagnosing patients intoxicated with SCRA.

Conclusion

Recreational drug use is a significant healthcare burden in MDH. Although the number of admissions is relatively small, these appear to be on the increase, with a substantial increase in 2015. More than half of such patients were confused (GCS<15), and 16.4% needed critical care.

'Classical' recreational drugs are the most common recreational drugs associated with admissions. NPS however have become an important threat from a public health perspective. More than a third of all admissions in 2015 involved a NPS (SCRA or synthetic cathinones). A large proportion of the SCRA-associated admissions were severe, with respiratory depression, acidosis and low GCS. Although SCRA symptoms appeared to improve relatively quickly, a third of patients with lone SCRA intoxication had AKI, 16.7% had seizures, and more than a quarter of such admissions needed critical care.

The use of the toxidrome mnemonic 'MEET_SCRA' is proposed in order to facilitate patient diagnosis in cases of SCRA intoxication.

Limitations

Since admission records was obtained from a clinical coding system based on discharge letters, admissions that had no discharge letter done were not included. Such might have occurred if the patient self-discharged or died during that admission.

This study only included patients admitted to MDH. While the admissions likely reflected those patients that had the more severe symptoms, it also excludes a large cohort of patients that were discharged from the ED.

This study was based substantially on the self-reporting of recreational drugs taken, and this also depends on the patient's attitude towards possible legal repercussions.

There is currently no available LC-MS/MS in Malta, thus, SCRA and some other NPS could not be detected.

The mass spectrometer of the GC-MS in the MDH laboratory was not operational from mid-2015 onwards, due to a malfunction. This might have resulted in less reported NPS in the latter half of 2015.

Recommendations

Further research on the pharmacology and toxicology of recreational drugs including NPS, and their impact on hospitals locally and internationally is recommended.

The use of the toxidrome mnemonic 'MEET_SCRA' is proposed in order to facilitate patient diagnosis in cases of SCRA intoxication.

A LC-MS/MS and a better-equipped hospital laboratory would be a valuable asset in early identification of recreational drug outbreaks, such as with SCRA in 2015.

In 2016, Malta joined the Euro-DEN project[25] which aims to identify recreational drug use presenting to European ED's. Such data can be of help to local and EU policy makers, when deciding on future healthcare implementations on this subject.

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Ethics approval

University Research Ethics Committee (University of Malta).

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Original Article

Breaking Bad News in Cancer: An Assessment of Maltese Patients' Preferences

Joëlle Azzopardi, Dorothy Gauci, Patricia A. Parker, Neville Calleja, Jeff A. Sloan, Raymond Zammit

Abstract

Purpose: It is unclear whether Maltese cancer patients wish to know their diagnosis or to what extent they want to be informed.

The aim was to assess patients' preferences for receiving a cancer diagnosis and being involved in the decision-making process, and then compare these with results from similar international studies.

Methods: Two hundred fifty-two Maltese adult cancer patients were invited to complete two standardised tools: the Measure of Patients' Perspective (MPP), assessing patients' preferences for receiving news about their cancer, and the Control Preferences Scale (CPS), examining involvement in decision-making.

Results: Maltese patients rated the 'content' subscale (information given; mean 4.17, SD 0.59) as significantly more important (p<0.001) than 'support' (offering comfort/support; mean 3.73, SD 0.68) and 'facilitation' (how information is given; mean 3.86, SD 0.68). Patients with higher levels of education had significantly higher scores for 'content' (p=0.018) and 'facilitation' (p<0.001) on the MPP, while lower education levels preferred a passive role (p=0.01) on the CPS. Although there is a trend towards a collaborative and even an active role in treatment decisions, patients still exhibit a paternalistic attitude towards their physician. Age, gender and medical variables had no significant influence on response.

Conclusions: Maltese cancer patients want to be informed of their cancer diagnosis, its treatment and prognosis, similar to other international studies. However, 60% of Maltese patients prefer a

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more paternalistic approach towards their physician when compared to other studies.

Keywords

patient preference, patient rights, health literacy, decision making, neoplasms

Introduction

Cancer is a significant disease in Malta, with 1200 Maltese residents presenting with new cancers each year (Malta National Cancer Registry 2002). A diagnosis of cancer goes hand in hand with breaking bad news, which is usually delivered by hospital doctors as the majority of investigations are hospital-based. To break bad news effectively, physicians must devote time to the patient, giving information accordingly, answering any questions that may arise, and dealing with the aftermath of such disclosure. Truth-telling is becoming increasingly advocated and offers far-reaching benefits to all involved.[1]

Background

From a medical point of view, bad news has been defined as:

> "any information which adversely and seriously affects an individual's view of his or her future".[2]

This can be viewed on two levels: a level at which life is temporarily interrupted, such as replacing a hip joint, and a deeper level which threatens the continuity of life, as is the case with malignant disease.[3] Unfortunately, the field of oncology is riddled with bad news, ranging from disclosure of a diagnosis, through treatment failure, to recurrence of disease and end of life issues. The way bad news is broken can have a profound effect on improving patients' compliance with treatment, may lead to a clearer understanding of instructions or symptoms, may help reduce stress and anxiety, and improve overall patient satisfaction.[4-5] On the other hand, delivered inappropriately or insensitively, bad news may exert a lasting impact on the ability to adapt and adjust, whilst also inviting the risk of litigation.[6] Inappropriate delivery of unfavourable news includes usage of unfamiliar medical jargon or giving scanty information. Recipients of such messages may feel confused, anxious or angry.[3]

In recent decades there has been a dramatic shift towards disclosure of cancer diagnosis in Western Countries, especially in North America, Australia and most of Europe.[5] The previous paternalistic attitude favouring concealment in order to protect the patient has become overshadowed by the growing importance of safeguarding patient autonomy.[7] Patients are considered to have a moral and legal right to receive accurate and reliable information, and it remains the doctor's responsibility to deliver the diagnosis accurately and explain treatment options clearly.[3] The content of discussions needs to be honest so that patients can provide informed consent about their treatment.[6] This has undoubtedly been a step in the right direction – patients are now better informed and more respected.[7]

There is no data regarding the standard practice about truth telling to patients in Malta. Only recently, a Patient Charter document was brought into effect locally. Principle 4 of the Charter deals with Shared Decision-Making and Informed Consent, specifying that "one has the right to participate in the collaborative process of decision-making related to one's particular health-care needs and to make an informed consent about one's treatment and care".[8] Our research therefore fits in with the climate in which changes are being made locally in the field of shared decision-making.

Patients and methods

Participants and Procedures

The intention of this cross-sectional survey was to investigate preferences for truth-telling about cancer and involvement in treatment decisions among Maltese cancer patients aged eighteen and over. With a total Maltese population of a little over 400,000 people, Malta has one oncology centre, and the out-patient follow-up clinics were therefore considered an ideal location for recruiting patients for the study.

A consecutive sample of oncology patients were approached in the waiting area by the researcher who was not a member of the oncology team, and were invited to voluntarily complete an anonymous questionnaire in Maltese which would take around twelve minutes. The self-completed questionnaire was presented as a seven-page booklet consisting of an information sheet for patients, demographic and medical data to be filled by the patients and caring physician, and the questionnaires themselves. Field work was carried out every day for two consecutive weeks. The researcher was available at all times to answer any queries and respondents were also furnished with a leaflet about the nature of the study, and contact details of the researcher. Data was collected by quantitative methods.

Inclusion criteria were: diagnosis of any type of solid tumour cancer at least a month prior to interview, having received at least one type of treatment (chemotherapy, radiotherapy, hormonal or other therapy), awareness of a cancer diagnosis and Maltese literacy. Exclusion criteria were: aged younger than eighteen, non-natives, non-cancer diagnosis, and diagnosis less than one month prior to fieldwork. Prior to commencement of research, permission was sought from the Data Protection Board and University Research Ethics Committee (UREC) of the University of Malta.

Two hundred sixty-nine patients were approached to participate in the study, of which seventeen met the exclusion criteria. All the returned questionnaires were valid, in that most responses had been filled in and could therefore be used for analysis. The questionnaire delivered to patients was bipartite, consisting of the Measure of Patient Preferences (MPP) Questionnaire and the Control Preferences Scale (CPS). The thirty-two-item MPP, scored on a five-point scale (1-5) and initially developed in the United States by Parker *et al.*, was used to assess preferences for characteristics of the bad news encounter. Preferences relate to three aspects: ‘facilitation’ - the setting in which the news is delivered; the ‘content’ of the message; and the ‘support’ offered.[4] To understand to what degree patients are being involved in the decision-making process, the two-item Control Preferences Scale (CPS), developed in Canada by Degner *et al.* was used.[9] This five-point (A-E) self-reported scale assesses patients’ preferences for control in medical decision-making, ranging from a wholly active role (A) through to a wholly passive role (E). The tool allows respondents to portray how they were involved in treatment decisions (CPS-1), and then to express how they would have liked to have been involved (CPS-2).

Outcome Measures

Permission was obtained from the authors of the MPP and CPS to utilise their questionnaire, who are also authors of this research. The questionnaires were translated from English into Maltese by a senior lecturer of the Maltese language, followed by conceptual translation to ascertain that concepts were understood in the same way, and to ensure cultural acceptability of the questionnaire. The corrected questionnaire then underwent cognitive debriefing whereby it was actively tested among representatives of the target population to assess whether the questionnaire was being understood in the same way as the original would have. Following the amendments made, the product tool was considered to be reliable for usage in the Maltese sample population. Validity testing was not necessary since this had already been done by Parker *et al.*, and Degner *et al*. in their respective studies which produced the MPP and CPS. The questionnaire was then pilotted prior to actual usage.

Demographics and Medical Data

Demographic information, including gender, age, marital status and educational level was collected. Participants supplied information on stage of disease and recurrence status, while their physicians gave additional information on cancer type, date of diagnosis, stage of disease and recurrence, and treatment given (Table 1).

Statistical Analysis

Descriptive statistics were presented for demographic and medical characteristics of the sample, while univariate analysis was conducted to examine independent associations between respondents' demographic and clinical characteristics, and the MPP and CPS data. Since the MPP is assessed through scores, tests for differences between means were used. T-Tests and one-way ANOVA were used as applicable. For the CPS categorical data, odds ratios (OR) were used to assess independent associations between the demographic variables and CPS category. These associations were then assessed using multinomial regression analysis while adjusting for any possible confounding factors.

For all tests, a $p<0.05$ was used to assess statistical significance, and confidence intervals (CI) of 95% were presented as applicable.

Results

Two hundred fifty-two patients were eligible to participate in the study, of which forty-two were physically, cognitively or psychologically unable to complete the questionnaire, and 11 refused to participate. Thus, the participation rate was 79%, similar to that obtained in other studies which registered similar eligibility criteria.[16] Patients who refused to participate did not differ by age ($p=0.758$) or gender ($p=0.993$) when compared to respondents.

The mean time from diagnosis to completion of the questionnaire was 52.3 months (4.4 years), somewhat more than that in Parker *et al*.'s study (3.3 years),[4] the long duration resulting from the prolonged follow-up necessary before a patient can be declared disease-free. There was no statistical significance between those with a recent or distant diagnosis. Some had received bad news twice, once on diagnosis and again on recurrence.

Females accounted for 67.3%, and the age range of participants was 27 to 86 years (mean 62.2 years; SD 12.6 years), similar to that observed in the Canadian population study (mean 62.4 years, SD 8.4, range 46-85),[14] and the Japanese population study (62 years, SD 11, range 26-97).[16] Of note, less than a fifth had completed tertiary education, which was similar to a British study where 20.0% had attended college or received a graduate degree.[13]

Table 1: *Demographic and medical characteristics of the population sampled*

Characteristics	**% (n)**
Mean time from diagnosis	4.4 years (SD 4.48)
Gender (*n*=199)	
Male	32.7 (65)
Female	67.3 (134)
Mean Age (*n*=199)	62.2 years (SD 12.6 years)
Marital Status (*n*=199)	
Married/Living with Partner	68.3 (136)
Widowed	12.6 (25)
Single	12.6 (25)
Separated/Divorced	6.5 (13)
Level of education reached (*n*=197)	
Primary	41.6 (82)
Secondary or Post-Secondary	41.1 (81)
Tertiary or Post-Graduate	17.2 (34)
Employment Status (*n*=198)	
Domestic Tasks	40.9 (81)
Retired	31.3 (62)
Employed	24.3 (48)
Unemployed	3.5 (7)
Cancer Type (*n*=196)	
Breast	37.8 (74)
Gastrointestinal Tract	13.8 (27)
Prostate	9.2 (18)
Gynaecologic	7.1 (14)
Urological	7.1 (14)
Haematological	6.6 (13)
Lung	5.6 (11)
Thyroid	5.6 (11)
Other cancers	7.1 (14)
Cancer Recurrence (*n*=196)	
Yes	21.9 (43)
No	78.1 (153)
Mean time	2.49 years (SD 2.68)

Several types of cancers were represented in the population sampled, including rare cancers, reflecting the distribution of cancer types in the Maltese Islands, being similar to those found in the Italian population study[15] (Table 1). The large majority of respondents (91%) accurately reported their diagnosis, and 36.7% were able to stage their disease. More males (72.3%) tended not to know their stage compared to females (60.4%), but this was not significant (*p*=0.101). Younger patients were more likely to know their disease stage than older ones (*p*=0.017). Of the 71 patients who documented a stage, 16 had no physician-listed stage to compare to. 60% of the remaining reported the correct stage, while 59% of incorrect answers quoted a less advanced stage of disease. Most of the patients received at least two types of treatments/interventions, with surgery being the most common (Table 2).

***Table 2**: Percentage distribution of surgical and anti-cancer treatments which patients received (patients could have had more than one treatment/intervention)*

Surgical and anti-cancer treatments	**% (*n*)**
Surgery	70.9 (141)
Radiotherapy	57.1 (114)
Hormonal Therapy	44.9 (89)
Chemotherapy	41.3 (82)
Palliative	2.6 (5)
Other	9.2 (18)

'Recurrence' in this study refers to the re-appearance of a previously quiescent disease, or advancement of disease which was previously stable. Just over a fifth (21.9%) had had a recurrence by the time of the survey, which is less than those observed in an American (31%)[4] and British population (52.7%)[13]. The mean number of months from diagnosis to recurrence was 29.9 months (SD 32.2 months).

MPP

The highest scoring item was ranked at 4.35 (SD 0.81), which comes close to results from the American (4.72, SD 0.49)[4] and British (4.62, SD 0.67)[13] studies. Table 3 represents the ten highest and lowest scoring items on the MPP, with seven out of the highest and six out of the lowest scorings being common between the Maltese, American[4], and British[13] studies. The lowest scores in this study nonetheless ranked greater than 3.0, indicating that all items in the questionnaire were considered important by respondents.

The same three categories as those identified by Parker *et al*.[4] were used in this study: 'Content', 'Support' and 'Facilitation'. The mean score for 'Content' was 4.17 (SD 0.59), for 'Support' 3.73 (SD 0.68) and for 'Facilitation' 3.86 (SD 0.68). These results were mirrored by those obtained in American[4], British[13], and Canadian[14] studies. The mean score for 'Content' was significantly higher compared to 'Support' ($p<0.001$) and 'Facilitation' ($p<0.001$).

When considering demographic and medical characteristics of the population *vis-a-vis* the MPP category scores, education proved to be the only significant predictor, significantly associated with the 'Content' ($p=0.018$) and 'Facilitation' ($p<0.001$) sub-scales. Those with primary education reported a lower average 'Content' score than those with tertiary education ($p=0.021$), and likewise for 'Facilitation' in both the primary ($p<0.001$) and secondary education ($p=0.002$) sub-groups, hence suggesting that those with tertiary education place more importance on the 'Content' of the physician-patient dialogue and on how and where bad news is broken ('Facilitation'). These results are in-keeping with those obtained from the American study, where education significantly predicted scores on the 'content' and 'facilitation' subscales.[4]

CPS

Two-thirds of respondents (68.2%) experienced a passive role, with a quarter (25.9%) having a collaborative role, and only 5.8% an active role (CPS 1). In CPS-2, although the passive role remains the most popular, this drops from 68.3% to 59.7% indicating a shift to the collaborative and active role (Figure 1). None of the patients' demographic or medical characteristics increased the likelihood of having either role compared to a passive role (reference group) in CPS-1.

__Table 3__: Highest and lowest MPP ratings

Highest ratings MPP	**Mean (SD)**
My doctor describing all of my treatment options in detail	4.35 (0.81)
My doctor telling me the best treatment option	4.35 (0.75)
My doctor being up to date on research on my type of cancer	4.34 (0.69)
Having my doctor take the time to answer all of my questions completely	4.32 (0.77)
Having my doctor give me his/her full attention	4.25 (0.83)
Being given enough time to ask all of my questions about my cancer and the available treatments	4.24 (0.74)
My doctor letting me know all of the different treatment options	4.21 (0.77)
Having the doctor be honest with me about the severity of my condition	4.19 (0.92)
Waiting until all test results are in and he/she is certain about the news before telling me	4.17 (0.85)
Being given detailed information about the results of medical tests	4.14 (0.80)
Lowest ratings MPP	
My doctor telling me about support services that are available to me	3.82 (0.88)
Being told in person rather than over the phone	3.71 (1.11)
Being told in a private, quiet setting	3.69 (1.07)
Telling me it's ok if I become upset	3.66 (0.95)
Having the doctor tell me about resources in the community	3.57 (0.96)
Having the doctor inform my family members about my prognosis	3.52 (1.14)
Having another health care provider present to offer support and information	3.51 (1.08)
Having the doctor inform my family members about my diagnosis	3.49 (1.17)
Having my doctor maintain eye contact during the meeting	3.39 (1.12)
My doctor helps me to figure out how to tell my family and friends about the cancer	3.38 (1.17)

However, in CPS 2, there was a significant difference between primary and tertiary education (p=0.028); those in primary education were 81% times less likely (95% CI 0.04 – 0.84) to desire an active role than a passive role compared to the tertiary education group. These results mirror the preferences of British patients,[13] yet contrast with Canadian patients, where education had no significant effect on the preferred role.[14] This demonstrates a desire for an increasingly active role with increasing levels of education. None of the other univariate analyses of independent associations were significant.

Since age and gender probably influence education level, a multivariate analysis adjusting for these two variables was conducted, revealing a more significant p-value (p=0.01), an OR of 0.12 and a narrower CI (0.26-0.60) (Table 4).

Figure 1*: Distribution of responses for each of the items CPS 1 (n=187) and CPS 2 (n=191). Error bars indicate 95% confidence intervals around the proportions.*

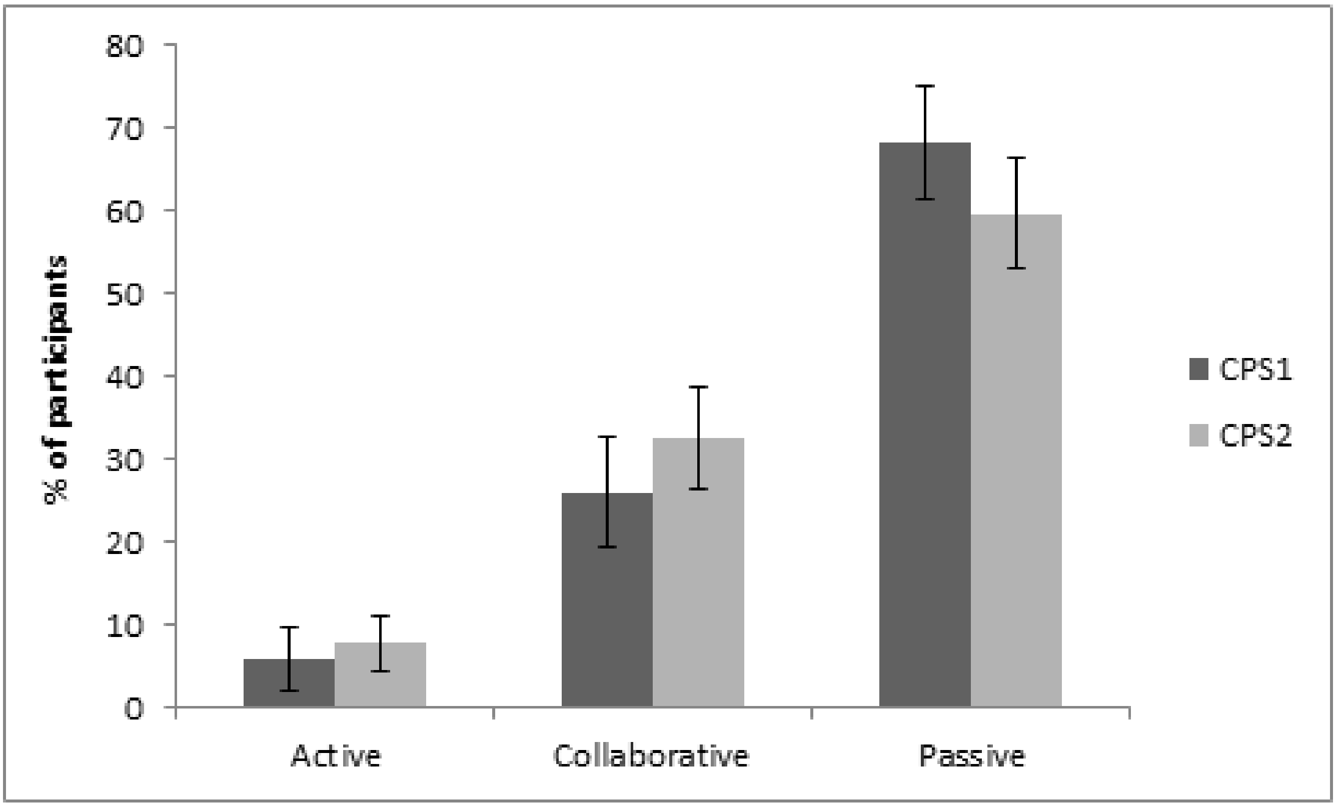

Table 4*: Final multivariate model for predicators and CPS2 as outcome. Passive is the reference group*

	Active		Collaborative	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender				
Male	0.78 (0.23 - 2.60)	0.685	0.97 (0.50 - 1.89)	0.928
Female	Ref	-	Ref	-
Age	1.04 (0.99 - 1.10)	0.1	0.99 (0.97 - 1.02)	0.661
Education				
Primary	0.12 (0.26 - 0.60)	**0.01***	1.32 (0.48 - 3.63)	0.585
Secondary/Post-Secondary	0. 43 (0.12 - 1.54)	0.193	1.59 (0.61 - 4.12)	0.344
Tertiary/Post-Graduate	Ref	-	Ref	-

Discussion

This study covered a representative sample of patients from the only oncology hospital in Malta, ensuring that patients with a range of disease characteristics and from different educational backgrounds were eligible for recruitment. Results can thus be regarded as reflective of the experience of Maltese oncology patients.

Malta stands out in that, at present, there is no robust framework in place to help patients. In fact, the 2014 European Union Health Literacy (HL) Survey 16 (EU-HLS 16) revealed that 42.5% of Maltese considered themselves to have a 'problematic' level of HL, compared with 35.2% in the EU. Likewise, only 9.2% of the Maltese sample graded themselves as having 'excellent' HL, as opposed to 16.5% in the EU.[11] The EU-HLS 16 for Malta echoes the main finding in our study – that level of education plays a vital role in choices patients make regarding their treatment, with statistical significance for the degree of HL at all education levels.

The CPS tool revealed that Maltese patients prefer a passive role in their treatment. This may change once legislation regarding patients' rights is implemented. Creating a climate of increased awareness and availability of information may tip the balance towards Maltese patients becoming more emancipated in their health choices. The nation's focus should change towards what can be done to improve health literacy. Since 7.6% of the Maltese population is illiterate,[12] providing information to the population by audio and visual means will ensure equity for all.

There were a number of limitations to this study. The MPP subscales were developed for an American population,[4] therefore extrapolating them to a Maltese population may not wholly reflect the cultural and treatment protocol differences within countries. However, the tool was successfully applied in a number of countries including in Europe, reflecting flexibility of the tool.[13-18]

Excluding some subjects from the study may have overlooked additional needs that these may have had, and possibly a different experience when compared to participants.

Diagnosis was occasionally made several years prior to the study whereby respondents' memories may have faded, introducing recall bias. Furthermore, having re-experienced breaking bad news allowed some subjects increased ability to give feedback, which may also have introduced an element of bias, as subjects were not asked to specify which experience they were referring to. In retrospect, those with a recurrence could have been excluded, and more patients recruited so as not to lose the power of the study.

Studies amongst Maltese cancer patients tend to be small due to our limited population size. This makes sub-group analysis difficult to power. To mitigate this, categorical dummy variables were created to ensure meaningful comparisons, while allowing for statistical power. The study applied a cross-sectional design yet informational needs may change over time.[19] Future research may investigate how these may vary throughout the patient experience.

Conclusion

For Maltese patients, education level is a key factor influencing their preference for the type and amount of information they receive. Considering that the EU-HLS 16 has shown a percentage of the Maltese population with a problematic level of HL, our MPP results are of relevance as they demonstrate that education plays a crucial role in treatment choices patients make.

Similarly, utilising the CPS revealed that Maltese patients overtly prefer a passive role in their treatment. As local legislation is implemented, this study can bolster support for initiatives to improve HL and increase awareness of patients' rights, empowering patients to take an active or collaborative role in treatment decisions. This should lead to better patient satisfaction and hence improve supportive care to cancer patients.

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A local perspective on basal cell carcinoma: frequency of subsequent skin tumours

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Abstract

Background: Basal cell carcinoma (BCC) is the commonest skin malignancy with a significant risk of recurrence and new primaries. The major risk factor is ultraviolet (UV) radiation, which is relevant to Malta, where the UV index is frequently high.

Objective: The aim of this study was to follow up patients diagnosed with BCC, analyse the occurrence of subsequent malignant and pre-malignant skin tumours and assess whether variables like age and gender modify risk. This will aid local screening methods and follow-up protocols.

Method: Patients registered with BCC in the Malta National Cancer Registry in 2007 were included in our study. Histology results belonging to these patients were followed up until the end of 2014. Risk of developing further lesions when accounting for age and gender was calculated using the Chi^2 test for Independence and hazard ratios.

Results: A total of 382 patients were diagnosed with BCC in 2007. Almost one third of these patients (30.1%) had at least another skin tumour biopsied thereafter; 71.7% of these tumours were BCCs. Squamous cell carcinomas and actinic keratoses were also commonly biopsied. Nine patients developed malignant melanoma. The commonest location for BCCs and other non-melanoma skin tumours was the face. Males and the elderly had significantly higher risks to develop further skin tumours, as reflected by our statistical data.

Conclusion: Our results are consistent with international data. BCC fulfils most criteria for screening, thus follow-up in high risk patients is recommended.

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Keywords

Carcinoma, Basal Cell; Follow-up studies; Malta; Risk factors; Skin neoplasms

Introduction

Basal cell carcinoma (BCC) is the commonest skin malignancy, and incidence rates are increasing. Individuals with a history of BCC have increased risk of developing new lesions especially in high-risk regions like the face. Although rarely metastatic and overall slow-growing, BCC may cause aesthetic and possibly functional complications from extensive local tissue destruction. The major risk factor for the development of BCC is exposure to ultraviolet radiation.[1] This has important implications for the Maltese Islands, where the UV indices can go up to very high levels during the spring and summer seasons.[2]

The purpose of this project was to obtain a local perspective on the frequency of new malignant and pre-malignant skin lesions in patients with past BCC and assess whether variables such as age and gender modify risk. This information will provide more knowledge to aid follow-up protocols and screening methods for patients with BCC.

Method

This was a retrospective study, using data from the Malta National Cancer Registry (MNCR) at the Department of Health Information and Research, with the approval of the Data Protection Unit. The MNCR indexes every histopathological confirmation of cutaneous BCC on a yearly basis, gathering reports from all laboratories across the Maltese Islands, most of which come from the Pathology Department of the main general hospital, Mater Dei.

In this study, we included all those patients recorded in the MNCR to have BCC in the year 2007. Data extracted from this list included age at time of diagnosis, gender, date of death for deceased patients, as well as the site and morphology of the BCC. This data did not include information about completeness of margins of excision.

In order to assess whether this cohort of patients developed other skin tumours after 2007, a search for the relevant histopathology reports was performed on iSoft Clinical Manager (iCM), the local electronic database that records patients' investigations. All histopathology results showing skin tumours (pre-malignant and malignant) were included up to the end of 2014. From these reports we gathered the following data: the number of cutaneous malignant and pre-malignant lesions confirmed by histology per individual, the site and morphology of these lesions, and the completeness of the margin of excision.

All data was organised in a spreadsheet and analysed with the software Stata® 11.2 (StataCorp LLC, Texas). For all statistical analyses, confidence levels of 95% were applied and *p*-values of less than 0.05 were taken to be statistically significant.

The Pearson's Chi-Square Test for Independence was used to assess for a relationship between gender and the likelihood to have further skin tumours. The Kaplan-Meier survival estimate was used to measure the time between the initial BCC and development of the first skin malignant or pre-malignant lesion biopsied thereafter, looking for a significant difference between males and females. Hazard ratios (HR) for gender and age in relation to the amount of time passed to the second skin tumour were calculated using a Cox Regression analysis, adjusting for ties with the Breslow Method. A ratio more than one was taken to imply increased risk.

For the deceased patients, the Chi-Square test for Goodness of Fit was used to analyse the difference between the observed and expected number of deaths, correcting for gender. Data was entered into a contingency table, placing male and female variables in rows, and alive and deceased variables in columns. The expected values of deceased patients for each gender were calculated by multiplying the row total with the column total, and dividing that against the total number of patients. In this analysis one patient had to be omitted as the date of death was also the date of incidence.

Results

Demographic analysis

A total of 382 patients were diagnosed with BCC in 2007; no patient was found to have more than one BCC biopsied in that year. The age ranged from 16-93 years at the time of diagnosis. The mean age of presentation was 66.2 years (see Figure 1). Out of the 382 patients, 115 (30.1%) had further skin tumours biopsied on follow-up, whilst 267 patients (69.9%) had no further biopsies documented. Those patients who developed subsequent skin tumours had a slightly older mean age (69.2 years) when compared to the general study population. In this study, four patients were younger than 30 years at initial presentation. They had no further documented biopsies in the follow-up period; three of these four patients were female.

The majority of patients presenting with a BCC in 2007 were male (n=227, 59.4%). When the Chi-Square Test for Independence was used to assess for a relationship between gender and the likelihood to have further tumours, a Chi^2 value of 11.093 and p-value of <0.001 were obtained, implying that males were significantly more likely to have further skin tumours.

The Kaplan-Meier estimation (Figure 2) shows marked separation between the female and male groups; thus, the time to develop a second skin tumour after the first BCC is significantly shorter for males. When the Cox regression model was applied to assess the effects of gender and age on the time to develop a second skin tumour, the following values were obtained: HR of 1.84 and p-value of 0.004 for male gender, and a HR of 1.02 and p-value of 0.016 for age. These hazard ratios suggest that the two variables have a causative effect on the time to second tumour, especially male gender.

Figure 1: *Distribution curve of the age of the patients presenting with BCC in 2007*

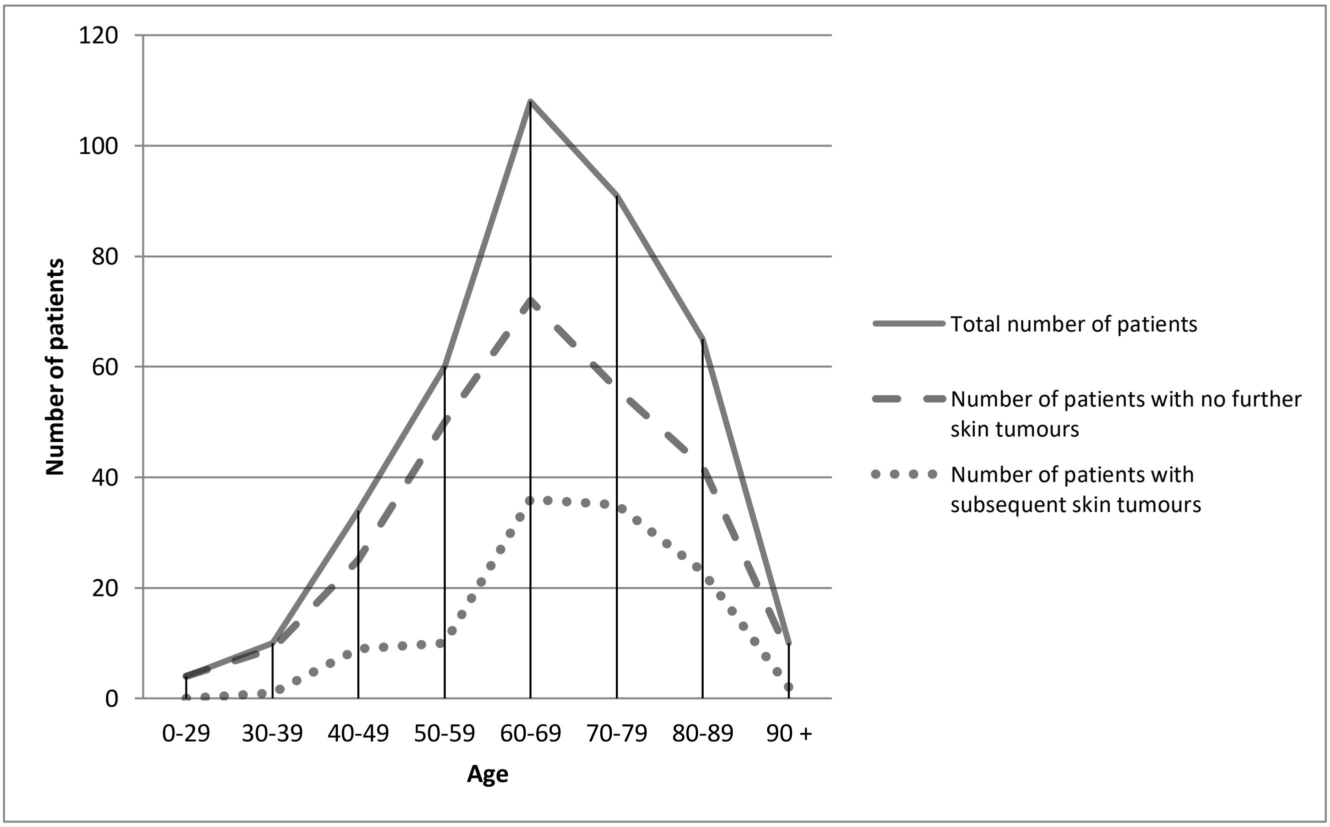
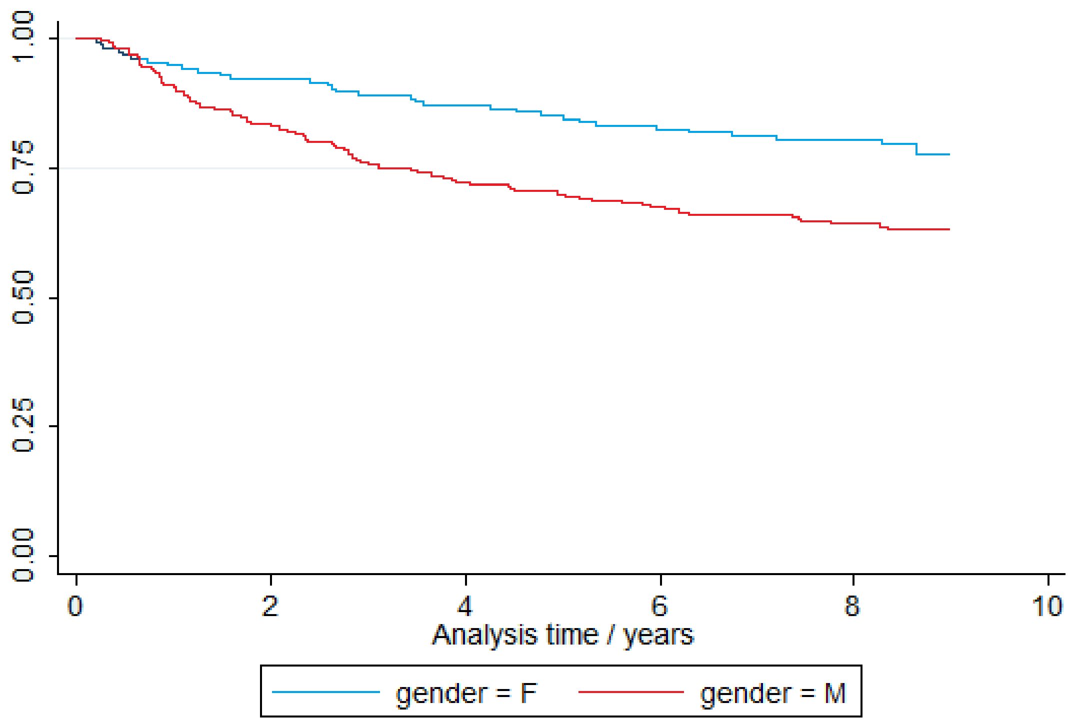


Figure 2: *Kaplan-Meier Estimation for time between first BCC in 2007 until first skin tumour biopsied thereafter according to gender*



At the time of the study, 18.6% of the 382 patients were deceased (*n*=71). When the Chi-Square test for Goodness of Fit was applied, a Chi ^2 value of 2.486 was obtained, with a *p*-value of 0.115. This implies no statistical difference in the number of deaths when correcting for gender.

Analysis of the skin tumours biopsied after 2007

In those 115 patients with further skin tumours, a total of 460 skin tumours were biopsied and sent for histopathology during the follow-up period (refer to Table 1). Whilst the majority of these were BCCs (*n*=330, 71.7%), there was a mixture of other skin lesions, namely squamous cell carcinomas (SCCs), cutaneous malignant melanomas, actinic keratoses (AKs), keratoacanthomas and one Merkel cell carcinoma. Ten melanomas were excised from nine patients in this cohort.

All the tumours included in this study were analysed according to site (refer to Table 2). Of the BCCs excised in 2007, 66.8% were located on the head and neck. The next most common location was the trunk (11.3%). Of the BCCs excised after 2007, 20.3% were located on the trunk, 46.3% (*n*=31) of which were of the superficial type. From the BCCs sent for histology in 2007, 10.2% (*n*=39) were listed under the topographical code C44.9, meaning that the location of the biopsy was undocumented. In view of poor documentation, it was often difficult to recognise which BCCs after 2007 were recurrences at the same site as opposed to new primaries. Regarding the site of the cutaneous malignant melanomas, four of the ten melanomas in our study were located in the head and neck region (one on the face and three on the scalp/neck); the remaining six melanomas were distributed evenly on the trunk and lower limbs.

The number of malignant and pre-malignant skin tumours biopsied for each individual after 2007 is presented in Figure 3. Ten patients had more than ten skin tumours removed after 2007 (Table 3). One patient had 22 skin tumours removed in this seven-year period. No melanomas were biopsied in this group of patients. The medical records of these patients were reviewed for documentation of any risk factors explaining their high incidence of skin tumours. Documentation occurred in only two cases, both of which were noted to have a history of chronic sun exposure. Notably, there was only one female in this group of patients; she had a documented history of breast cancer and Sjogren's syndrome in addition to a history of sunbathing.

Our final analysis concerns the completeness of the margin of excision for the skin tumours biopsied after 2007 (refer to Table 4). Punch biopsy reports were only taken into consideration if the lesion was not subsequently excised. The percentage of BCCs reported to be incompletely excised and not followed by a subsequent wider excision was 8.8%.

Discussion

In our study we confirmed that the majority of patients presenting with BCC in 2007 were males older than 60. This is similar to trends in international data, although it is well-known that rates in females are on the rise in view of altered sun-seeking behaviour.[3] Some studies show that in younger patients the incidence of BCC is higher in females.[4] Although the number of patients younger than 30 years in our original study cohort was too small to draw accurate conclusions as there were only four, our findings seem to support this as three were female.

Table 1*: The number of malignant and pre-malignant skin tumours biopsied between 2008 and 2014, according to histology*

Histology	Number of skin tumours
Basal cell carcinomas	330 (71.7%) *(of which 47 were superficial BCCs)*
Squamous cell carcinomas	57 (12.4%)
Actinic keratoses	57 (12.4%)
Malignant melanomas	10 (2.2%)
Keratoacanthomas	5 (1.1%)
Merkel cell carcinoma	1 (0.2%)
TOTAL	**460**

***Table 2**: Sites of basal cell carcinomas biopsied in 2007 and of the skin tumours biopsied thereafter. Codes used are from ICD-O-3*

Topography Code and Anatomical Site		**BCC in 2007**	**BCCs between 2008 and 2014**	**Other malignant and pre-malignant skin tumours between 2008 and 2014**
TOTAL No. of tumours		**382**	**330**	**130**
C44.0	***Lip***	12 (3.1%)	6 (1.8%)	4 (3.1%)
C44.1	***Eyelid***	24 (6.3%)	8 (2.4%)	0
C44.2	***External ear***	20 (5.2%)	10 (3.0%)	9 (6.9%)
C44.3	***Face*** ***→ (Nose)***	183 (47.9%) -	166 (50.3%) *(47)*	49 (37.7%) *(8)*
C44.4	***Scalp, neck***	16 (4.2%)	18 (5.5%)	24 (18.5%)
C44.5	***Trunk***	43 (11.3%)	67 (20.3%) *(31 of superficial type)*	14 (10.8%)
C44.6	***Upper limb***	24 (6.3%)	20 (6.1%)	14 (10.8%)
C44.7	***Lower limb***	15 (3.9%)	28 (8.5%)	15 (11.5%)
C44.8	***Overlapping***	6 (1.6%)	0	0
C44.9	***Skin, Not specified***	39 (10.2%)	7 (2.1%)	1 (0.8%)

***Figure 3**: Histogram showing the number of malignant and pre-malignant skin lesions biopsied between 2008 and 2014 and the frequency of patients per number*

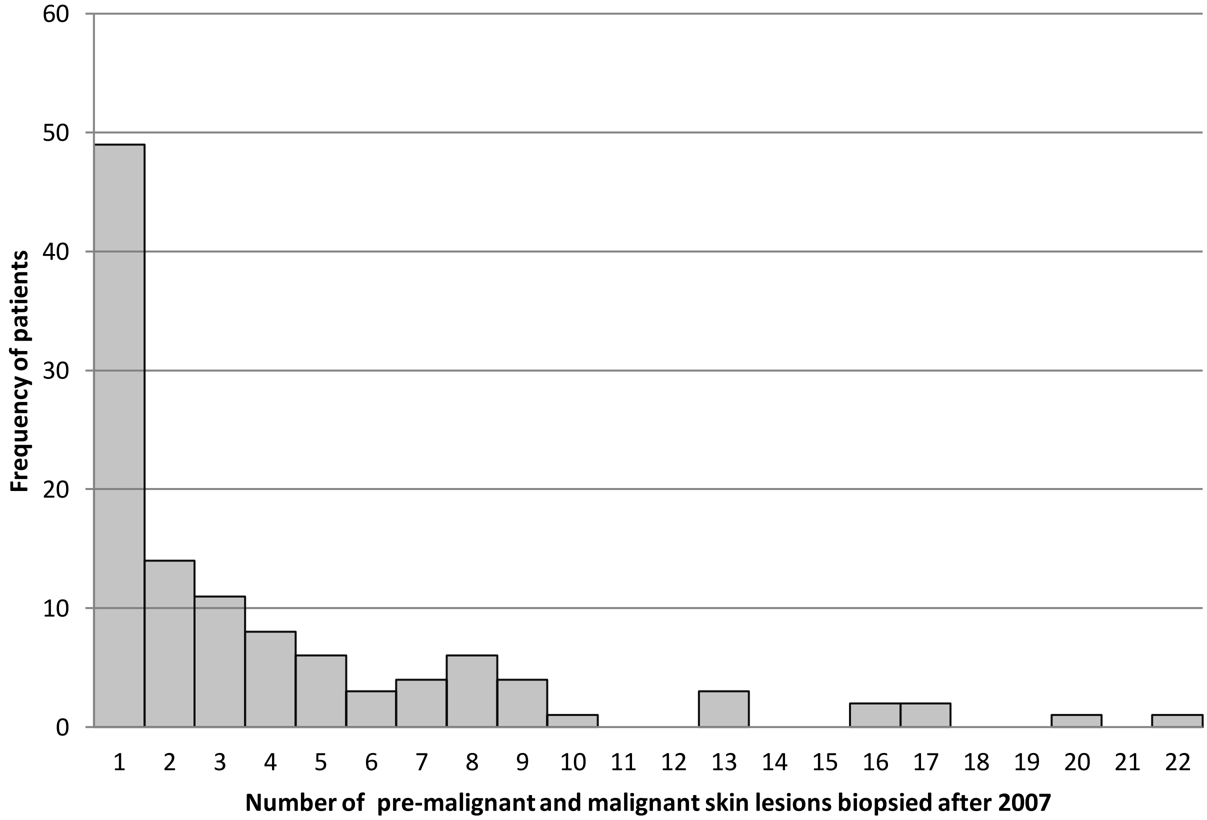


Table 3*: Patients who had 10 or more tumours biopsied between 2008 and 2014 after the presenting BCC in 2007*

Patient	**Gender**	**Age in 2007**	**Site of BCC in 2007**	**No. of subsequent BCCs (2008-2014)**	**No. of subsequent other skin tumours (2008-2014)**	**Documented risk factors**
1	M	77	Face	4	2 SCC 4 AK	Not documented
2	M	76	Face	9	4 AK	Deceased - records unavailable
3	M	62	Face	4	8 SCC 1 AK	Not documented
4	F	62	Not specified	8	2 AK	**History of sunbathing; Breast Ca; Sjogren's syndrome**
5	M	82	Face	11	2 SCC 3 AK	Not documented
6	M	69	Not specified	5	2 SCC 8 AK 1 KA	Records unavailable
7	M	76	Face	13	4 AK	Records unavailable
8	M	61	Face	10	2 SCC 5 AK	Not documented
9	M	77	Trunk	20	nil	Deceased – records unavailable
10	M	75	Face	18	1 SCC 3 AK	**Outdoor occupation documented**

Table 4: *Completeness of margin of excision for BCCs and other skin tumours biopsied between 2008 and 2014*

Margin of excision	**Basal cell carcinomas**	**Other skin tumours**	**TOTAL**
Complete	292 (88.5%)	85 (65.4%) (includes all 10 melanomas)	377 (82.0%)
Incomplete	29 (8.8%)	30 (23.1%)	59 (12.8%)
Unspecified or uncertain	9 (2.7%)	11 (8.5%)	20 (4.3%)
Punch biopsies	0	4 (3.1%)	4 (0.9%)
TOTAL	330	130	**460**

We have also found that 30.1% of the 382 patients diagnosed with BCC in 2007 had at least another skin tumour biopsied in the subsequent seven-year period; 71.7% of these were BCCs. This is consistent with other studies, demonstrating that a history of BCC increases the risk for new BCCs.[5-6] It was interesting to note that SCCs and AKs were regularly associated with BCCs, while only nine patients developed cutaneous malignant melanoma. Cutaneous SCCs tend to develop following chronic sun exposure, whilst melanomas are typically associated with sunburns in childhood and adolescence. The risk of BCC seems to depend on the ability of the skin to tan. Good tanners tend to develop BCC after chronic sun exposure, while poor tanners are at increased risk of BCC with chronic sun exposure as well as with intermittent sunburning.[7-8] Immunosuppression increases the risk to develop multiple skin cancers of all types (particularly SCCs) and worsens prognosis.[9] As expected with a tumour that rarely metastasizes, the presence of a BCC did not contribute significantly to mortality when correcting for age and gender.

Not only did males outnumber females in our original study population, but males were also more likely than females to develop subsequent skin cancers. This was especially highlighted in the ten patients who had more than ten subsequent skin tumours – nine were male. The most probable explanation is that males are exposed to heavier sun exposure from occupational and recreational activities. In our study, males also showed a shorter time interval than females to develop the next skin tumour.

The commonest site for BCCs was the head and neck region, as has been observed internationally.[1,3] However, 20.3% of BCCs occurring after 2007, as opposed to 11.3% in 2007, were located on the trunk. With regards to the ten recorded melanomas, six were located on the trunk or lower limbs. This emphasises the importance of not limiting examination to the head and neck when following up patients with BCCs, as skin tumours located on other parts of the body might be missed.

Our last observation is that the local percentage of incompletely excised BCCs was 8.8%. International rates cited vary from 4-16.6%,[10] however these statistics take into account the more accurate technique of Mohs microscopic surgery, which is unavailable in Malta. For SCCs and especially AKs, the rate of incomplete excision was higher, but these are usually clinically less well-delineated than BCCs. Of note is that all melanomas were completely excised. In clinical practice, when a BCC is reported to be incompletely excised, sometimes it is decided to follow up the patient for recurrence rather than perform a wider surgical excision. The decision in these situations would be taken on an individual basis, depending on the histology of the tumour, the location, any associated immunosuppression and patient preference. We have no data on how many of the tumours biopsied that were reported to be incompletely excised subsequently underwent treatment with cryotherapy, topical 5-fluorouracil, imiquimod cream, or radiotherapy.

This study has a number of limitations, such as the fact that it was done retrospectively based on available iCM data and relying on the number of skin tumours biopsied and sent for histology – in this study no patients were examined clinically. The prevalence and frequency of skin tumours between 2008 and 2014 reported here are likely to be an under-representation. Patients having further lesions excised and sent for histological analysis to private laboratories would not be available through iCM and therefore would not be included in this study. Patients might have developed further skin tumours which were misdiagnosed, or did not seek medical opinion. Finally, further skin tumours (including recurrences) might have been diagnosed by dermatologists, and treated with cryotherapy, 5-fluorouracil or imiquimod cream, without biopsy. This happens occasionally with very superficial non-melanocytic tumours like superficial BCC or Bowen's disease of the skin. Actinic keratoses are also not routinely biopsied before treatment with cryotherapy, 5-fluorouracil or imiquimod cream, but are typically biopsied when hypertrophic or resistant to treatment to rule out invasive disease.

A systematic review published in 2016 dwells on whether screening for early detection of BCC is worthwhile.[11] It concludes that BCC fulfils most of the WHO criteria for screening. Early diagnosis whilst BCCs are relatively small allows for less aggressive treatment options. This would be particularly relevant in the facial region, where the costs and morbidity associated with the removal of large, disfiguring and complex lesions may be significant. Naked-eye inspection and dermoscopy are all that would be needed for early detection, making screening potentially cost-effective.

Mass screening of the entire population is impractical. However, we propose that patients who are diagnosed with BCC and are at high risk of developing further tumours are offered regular follow-up. This would include immunosuppressed patients and those with more than one BCC at first diagnosis.[5] The incidence of subsequent BCC increases rapidly with the number of previous BCCs, so patients with a history of multiple BCCs would also benefit from regular and long-term follow-up.[6] Patient education is also paramount. Patients should be made aware of the significant rate of subsequent skin cancers and what they may look like, so that they may be vigilant and present early with any suspicious lesions that may develop.

Conclusion

In conclusion, our study shows that almost one third of patients diagnosed with a BCC in Malta developed subsequent skin tumours within a seven-year follow-up period. This risk is higher in males, the elderly and those who have had a previous BCC. Regular follow-up is recommended for such patients as well as for immunosuppressed patients.

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Review Article

Catheter ablation in atrial fibrillation – a burning issue

Samuel Meilak, Oscar Aquilina

Abstract

Catheter ablation has, over the recent years, become central to the management of atrial fibrillation. As the latest studies consistently demonstrate it safety and increasing efficacy, AF ablation is being performed in many centres worldwide, with a Class IA recommendation in those with recurrent symptomatic AF despite medical therapy. Concomitantly, continuous technological advances accompany the development on new electrophysiological techniques.

In this review, the authors seek to address the need among the local medical community of more in-depth knowledge of the technique and its indications, especially in view of the recent introduction of such service at our national hospital.

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia effecting two percent of the general population and one-in-ten octogenarians.[1] Around 8 million people are estimated to be effected in the EU, with the number predicted to double within the next half a century.[1] Whilst up to 40% of patients are asymptomatic, others may experience disabling symptoms, primarily palpitations.[2] Antiarrhythmic drugs provide effective symptom control in a further 30%, with the other half of symptomatic AF patients failing drug therapy.[2]

AF results from ectopic activity within the atria with subsequent complex multiple wavelet re-entry pathways.[3] Permanent AF is the most common type, present in up to one half of effected patients, with the rest suffering from paroxysmal or persistent AF.[1] This arrhythmia is associated with a negative impact on the quality of patient's lives, a five-fold increase in the risk of stroke, higher incidence of heart failure as well as elevated health care costs from hospitalisations, interventions and medications.[2]

Over the last two decades, AF ablation has evolved from a novel experimental procedure to a successful intervention performed at most large medical centres that provide a clinical cardiac electrophysiology service.

Local experience

Ablation for atrial fibrillation was

introduced locally in 2016 at Mater Dei Hospital. To date, 20 patients have undergone this intervention, with the majority being de novo cases. The technique used locally involves point by point radiofrequency ablation.

Management

Thromboprophylaxis is essential in the management of AF patients. Oral anticoagulation (OAC) can prevent ischaemic CVAs and reduce mortality in all patients except those at very low risk.[4]

The gold standard for risk stratification for thromboembolic events remains the CHA2DS2-VASc score, since its introduction in the 2010 ESC guidelines. The recently published 2016 guidelines have reduced to a Class IIa (level B) the indication for OACs in patients with one clinical risk factor (i.e. a CHA_2DS_2-VASc score of 1 for men, and 2 for women), and therefore treatment 'should be considered'. This decision was based on the fact that whilst there is increasing evidence regarding stroke risk in these individuals, this is based mainly on observed stroke rates in patients not receiving OAC. In CHA_2DS_2-VASc risk score of at least 2 in males, and 3 or more in females, evidence very strongly favours prophylaxic, with OAC maintaining a Class I (level A) recommendation.[4]

The role of biomarkers such as high-sensitivity troponin and NT pro-BNP as risk- stratifier is still being studied.[5] Various bleeding scores have also been developed, namely HAS-BLED, ORBIT and ABC. These tools should be used to identify and correct modifiable risks elements, but in general should not lead to withholding OAC. Unfortunately, OAC is too commonly withheld for reasons including bleeding risk, patient frailty and complexity of VKA monitoring, even though mortality and morbidity rates from stroke still exceed those from bleeding in the majority of such patients.[4]

Vitamin K antagonists (VKA) reduce risk of stroke by two-thirds and mortality by twenty-five percent.[6] Its narrow therapeutic range and the need of frequent monitoring and dose modifications may, however, prove challenging. Novel oral anticoagulants (NOACs) are a non-inferior alternative that eliminate such drawbacks.[7-8] In whom OAC is contra-indicated, left atrial appendage closure should be considered in order to reduce the risk of embolic strokes[4]. Aspirin with/out clopidogrel carries the same risk of bleeding as OAC without preventing strokes as effectively, and therefore antiplatelet therapy is not recommended.[9]

The primary aim of AF therapy remains that of achieving and maintaining sinus rhythm, in order to relief symptoms, improve exercise tolerance, reduce thromboembolic risk and prevent cardiomyopathy. Sotalol or flecainide are first line in healthy individuals, whilst amiodarone is the treatment of chose in patient with heart failure. In the presence of coronary artery disease, sotolol should be used.

Rate versus rhythm control has been studied in two major randomized trials, AFFIRM and RACE. There was no statistically significant difference in mortality between the two strategies, whilst the number of hospitalisations and adverse drug effects were lower in the rate control group. Both trials enrolled high risk patients with structural heart disease, and results therefore should not be extrapolated to healthy young individuals.[10]

Rate control strategy is an acceptable alternative whereby the ventricular response rate of AF. This can be achieved by the use of medications that act on the atrioventricular (AV) node, supressing electrical conduction. If medical treatment fails, a last-resort approach involves the insertion of a pacemaker (VVI) followed by ablation of the AV node. Such technique is relatively simple to implement, with both complication and mortality rate being low.[11] Patients, however, are rendered pacemaker dependent for the rest of their lives. Other comorbidities, such as the presence on heart failure, help determine the type of pacemaker used (uni- or bi- ventricular,[12] with/out ICD[13]).

Maintenance of sinus rhythm is the main goal of the rhythm control strategy. Whilst antiarrhythmic drugs are first line in the rhythm control strategy of AF, catheter ablation can effectively restore sinus rhythm in those with recurrent symptomatic AF despite medical therapy (Class IA recommendation).[4] In obese patients, since weight loss should be considered to reduce AF burden and symptoms (Class IIa recommendation),[4] radiofrequency ablation should be offered in conjunction with lifestyle changes that promote weight reduction.

Contraindications to the procedure include left atrial thrombus, contraindication to anticoagulation (required post-ablation), severe mitral valve disease or mechanical mitral valve prosthesis, severe pulmonary hypertension and pregnancy.[4]

Patients considered to be potential candidates for AF ablation should be referred for review by an electrophysiologist in an outpatient's setting and undergo various investigations a 12-lead ECG, 24-hour Holter, echocardiography and cardiac CT/ MRI. Clinical evaluation and a discussion with the patient including benefits, risks and alternative strategies are crucial.

Patients should be started on oral anticoagulants at last four weeks prior to this elective procedure, whilst antiarrhythmic drugs should be stopped to unmask abnormal electrical activity. Closer to the procedure, adequate hydration minimises the risk of contrast-induced nephropathy, management of medical co-morbidities should be optimised and consultation with an anaesthesiologist arranged to evaluate the airway and risks for general anaesthesia.

Peri-procedurally, access to the left atrium is obtained transfemorally via a trans-septal approach. An oesophageal probe allows temperature monitoring to minimise risk of oesophageal damage and electrodes placed on the chest wall provide the electrical field used to create an anatomic map of the left atrium. Intravenous heparin is administered at the start of the procedure and activated clotting time (ACT) analysed every thirty minutes, giving further boluses of heparin as required in order to maintain ACT above 300ms

Ectopic electrical activity in the pulmonary veins (PVs) has for long been considered the culprit in AF initiation. The aim of the primary intervention, therefore, is to segregate such substrate from the left atrium.[14] The primary technique in AF ablation involves isolation of the pulmonary veins (Class IIa recommendation) through the creation of sequential point-by-point radiofrequency lesions over a circumferential margin encompassing all four PVs.[15] Other regions may be ablated at repeat procedures, namely the atrial roof, cavotricuspid and mitral isthmi.

Computerised electro-anatomic mapping systems allow the operator to create a three-dimensional image of the left atrium and the PVs that may also be merged with computerised-tomography or magnetic-resonance scans acquired prior to the procedure. This enables real-time identification of electrical and anatomic targets. Intracardiac pacing and sensing provides electrophysiological data with the purpose of localising abnormal electrical activity and assessing the effectiveness of the ablation at isolating it.

An alternative technique to radiofrequency is cyroablation, that uses refrigerant N_2O to induce tissues necrosis. Both methods have their advantages and drawbacks, with cryoablation considered to be performed with more ease whilst RF ablation allows more manoeuvrability as well as applicability to re-do procedures. FIRE and ICE, a multicenter, randomized trial by Kuck et al., showed non-inferiority of cryoablation versus RF ablation in both primary efficacy and safety end-points. Procedure time was longer, but fluoroscopy time shorter in the radiofrequency group.[16] What was their respective success rates? Which technique will win the race rests on further technological developments and the reproducibility of the results.

Major complication rates have fallen below five percent in recent years. Cardiac tamponade, pericardial effusions, atrio-oesophageal fistula, stroke, transient ischaemic attack, persistent phrenic nerve palsy, pulmonary vein stenosis and death have been reported. Other minor complications include femoral pseudoaneurysms and artero-venous fistulae. In an analyses by Yong-Soo Baek et al.[17], persistent AF and duration of procedure were associated with higher rates of major complications.

Close follow-up of patients after ablation is important especially in the initial phase where both patients and physicians should be aware of the signs and symptoms of complications, enabling prompt referral for their management. AF recurrences are not uncommon, with further rhythm control therapy being reserved mainly for the symptomatic patients. All post-ablation patients should be reviewed at last once by an electrophysiologist during the first year post-procedure.

Observational studies indicate that the risk of thromboembolic event is low after AF ablation, yet data and risk stratification has been adopted from non-ablation AF cohorts. Patients should remain anticoagulated for at last two months after ablation. The decision for long term use of anticoagulants post-procedure should be based on general anticoagulation recommendations, the long-term risk of recurrent AF and the safety profile of anticoagulation.

Way forward

Ongoing advances in technique and technology are reflected in more durable PV isolation and lower rates of AF recurrence post-ablation. Ouyang F et al. [Circulation, 2010] reported only 6% of patients with complete PVI at repeat procedure using 1st generation radiofrequency catheters. Recent figures indicate up to 66% durability of PV isolation with 2nd generation RF technology.[18] The use of real-time contact force measurements has increased atrial arrhythmia freedom in comparison to a standard non-force sensing catheter (88% versus 66% of patients respectively), though this came at the expense of longer procedure and fluoroscopy time.[19] Ablation technique developments, such as the ‘CLOSE’ protocol, have also paved the way for better success rates as measured by post single-procedure freedom from atrial fibrillation or tachycardia.[20] The future is even more promising with 3rd generation devices providing more reliable temperature and EGM at the tip-tissue interface as well as temperature controlled irrigated RF ablation with high-resolution EGM. In addition, the advent of catheters using ultrasound and laser modalities may also contribute towards further improvements. Concurrently, better mapping technologies are being developed. With ever increasing success rates, ablation may in the near future become the first line treatment of choice. Data from the RAFT-2 study has demonstrated a lower rate of recurrence at two-year follow-up in patients undergoing RF ablation versus antiarrhythmic drugs.[21]

Conclusion

Atrial fibrillation is an increasingly common condition with a high burden on our health system. Further developments in techniques and technologies, together with data from recent studies, are reflected in the recently published 2016 ESC Guidelines for the management of atrial fibrillation. The principles of management, however, remain those of appropriate anticoagulation coupled with a rate or rhythm control strategy, with the aim of controlling symptoms and reducing morbidity and mortality.

To date, the mainstay of the rhythm control strategy is pulmonary vein isolation either by RF ablation or cryoablation. Alternatively, rate control has been shown to be a non-inferior option for the management of AF patients. The CHA_2DS_2-VASc score keeps its place as the gold-standard risk-stratification tool for thromboprophylaxic. Whilst most patient can be managed by their physicians, those with symptomatic AF should be referred for assessment by an electrophysiologist, especially if symptoms persist despite medical therapy.

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Corinthia Group Prize in Paediatrics, 2017

The Corinthia Group Prize in Paediatrics for 2017 was awarded to Dr Karl Bonello, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to Dr Bonello, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Bonello is seen receiving his prize from Professor Simon Attard Montalto, Head of Paediatrics, in the Medical School. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto