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The Emergency Contraceptive Pill

Victor Grech

"It is undesirable to believe a proposition when there is no ground whatever for supposing it true" – Bertrand Russell.

This editorial will confine itself to emergency contraception (ECP, "morning after pill"), which the World Health Organization (WHO) defines as "methods of contraception that can be used to prevent pregnancy in the first 5 days after sexual intercourse. ECP is intended for use following unprotected intercourse, contraceptive failure or misuse (such as forgotten pills, or breakage or slippage of condoms), rape or coerced unprotected sex".[1] Furthermore, this editorial will confine itself to ECP which utilizes (synthetic) sex hormones.

Briefly, there are three types of ECPs: combined ECPs containing both estrogen and progestin, progestin-only ECPs, and ECPs containing an antiprogestin (mifepristone or ulipristal). Progestin-only ECPs have now replaced the older combined ECPs as they are more effective with fewer side effects. The primary mechanism of ECP is the prevention of fertilization by the inhibition of ovulation. To date, the best available evidence is that these medications do not have any post-fertilization effects – such as the prevention of implantation – when used as defined above.[2] The most recent scientific evidence shows that ECP delays ovulation and does not prevent implantation nor does ECP cause the loss of implanted embryos.[3] Indeed, Germany's Catholic bishops have ruled that levonorgestrel (progestin) ECP is acceptable for the prevention of pregnancy in the setting of rape, a significant change in the usually conservative Catholic posture. This pronouncement cites the total lack of evidence to the effect that levonorgestrel ECP is abortifacient since there is no evidence whatsoever that it prevents implantation.[4]

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The possibility of the introduction of ECP in Malta has been raised – and greeted by storm. This ignores the facts that there are local equivalents that can and are being used as emergency contraception and that ECP can be delivered by fast courier to our doors. The additional fact that a form of ECP is centrally licensed within the European Union (EU) and can be imported under current local legislation is also being ignored.

The ECP issue, once raised was locally naturally instantly riven with tension. However, the scientific truth of the matter is that extant medical knowledge, up to the time of writing, has never demonstrated that this form of ECP prevents the implantation of a fertilized ovum (a conception followed by implantation). ECP therefore cannot, in any way be considered abortifacient. Hence, the matter has become needlessly fraught, with individuals and authorities sounding off on the subject with gross inaccuracies, clearly without reading the relevant scientific literature and the latest research. Indeed, WHO has stated that

> all women and girls at risk of an unintended pregnancy have a right to access emergency contraception and these methods should be routinely included within all national family planning programmes. Moreover, emergency contraception should be integrated into health care services for populations most at risk of exposure to unprotected sex, including post-rape care and services for women and girls living in emergency and humanitarian settings … As part of this core obligation, states should ensure that the commodities listed in national formularies are based on the WHO model list of essential medicines … including emergency contraception, is included in the core list of essential medicines.[1]

In the same publication, WHO also points out that "in some countries emergency contraception is not available on the false grounds that it causes

abortion".[1]

This is an editorial in the *Malta Medical Journal* and we are scientists who strive to adhere to the Baconian scientific method which comprises systematic observation, measurement, experimentation, and the formulation, testing, and modification of hypotheses. All of this is done within the Popperian scientific framework of falsifiable hypotheses. It is these precepts that lead us to practice evidence-based medicine. These dicta should serve "as a reminder of the need for bioethics to be based on current scientific literature as well as articles of faith and morals".[4] Blind statements that ECP can or possibly might cause implantation failure must be backed by evidence-based scientific literature – which (up to the time of writing) is nonexistent. Wild accusations simply will not suffice to sway anyone – scientific evidence must and should.

This article has deliberately steered clear of definitions of commencement of life and commencement of pregnancy since such definitions are moot to the tenet that ECP does not prevent implantation. This article has also deliberately foregone forays into women's rights. Again, these arguments are moot since ECP does not prevent implantation and is therefore not abortifacient. This article has also deliberately avoided detours into the morality of sex and the risk of sexually transmitted diseases in unprotected sexual encounters since these are not germane to the issue. The central tenet is that ECP "does not prevent embryo implantation and therefore cannot be labeled as abortifacient".[5]

This is despite the fact that some of these product labels continue to state that one of the modes of action "may be" the (unwarranted claim that a mode of action includes) prevention of implantation. Indeed, back in 2008, the International Federation of Gynecology and Obstetrics (FIGO) issued a statement that with levonorgesterol ECP, "pregnancies occurred only in women who took ECPs on or after the day of ovulation, while no pregnancies occurred in the women who took ECPs before ovulation, providing evidence that ECPs were unable to prevent implantation".[6,7] Furthermore, FIGO noted that "studies show that LNG ECPs have no such [inhibitory] effect on the endometrium, indicating that they have no mechanism to prevent implantation".[8,9] Moreover, FIGO also noted that "levonorgestrel did not prevent the attachment of human embryos to a simulated (in vitro) endometrial environment".[10]

FIGO further clarified[6]

- "Emergency contraception is not the same as early medical abortion. EC is effective only in the first few days following intercourse before the ovum is released from the ovary and before the sperm fertilizes the ovum. Medical abortion is an option for women in the early stage of an established pregnancy, but requires a different drug from levonorgestrel.
- EC cannot interrupt an established pregnancy or harm a developing embryo".[11-12]

FIGO therefore recommended that "language on implantation should not be included in LNG ECP product labelling" since there was no evidence whatsoever that this was a mode of action.[6]

FIGO noted the corollary that "the fact that LNG ECPs have no demonstrated effect on implantation explains why they are not 100% effective in preventing pregnancy, and are less effective the later they are taken. Women should be given a clear message that ECPs are more effective the sooner they are taken", before ovulation occurs.[6] In an updated statement in 2012, FIGO reiterated: "review of the evidence suggests that LNG [levonorgestreol] ECPs cannot prevent implantation of a fertilized egg. Language on implantation should not be included in LNG ECP product labeling".[13]

Clearly, citing a package insert which contains a myriad of biases that date back from 2006 and are thus based on data prior to 2005 is ludicrous given the plurality of robust studies published in peer reviewed journals since. This appears to be the stance blindly taken by several individuals and organisations in this country, who repeatedly cite an inaccurate package insert while ignoring abundant and unbiased scientific research, along with recommendations by respected international bodies such as WHO and FIGO.

The contention that this form of ECP does not prevent implantation is supported by several studies, one of which dates back to 2001, clearly stating that ECP works by "disrupting the normal development and/or the hormonal activity of the growing follicle only when LNG is given preovulatory. In addition, peri- and post-ovulatory administration of LNG did not impair corpus luteum function or endometrial morphology".[9]

Similarly "levonorgestrel, given as emergency contraceptive on the day of LH surge, does not disrupt either ovulation or progesterone production by the corpus luteum. The contraceptive mechanism of levonorgestrel at the time of LH surge does not include changes in the progesterone receptors or the endometrial receptivity biomarkers".[14] Likewise, "neither the magnitude nor the nature or direction of the changes [found in this study] endorses the hypothesis that LNG interferes with endometrial receptivity".[15] And finally, "levonorgestrel caused either only minor or no alterations in markers of endometrial receptivity".[16]

Withdrawal bleeding after ECP has also been cited as indicating that these medications are potentially abortifacient. Indeed, transient menstrual disruptions are not uncommon with about half of women who used levonorgestrel ECPs experiencing withdrawal bleeding within seven days if taken prior to ovulation.[17] However, if taken after ovulation, ECP may actually increase the luteal phase, delaying menstruation by a few days.[18]

All of these studies point to one indisputable fact: this form of ECP does not prevent implantation. Thus, "ECPs do not interrupt a pregnancy (by any definition of the beginning of pregnancy)",[6] not unsurprisingly since progesterone is the so-called pregnancy hormone. It is indispensable for pregnancy, a "pro-gestational" hormone, hence the name.

Yet another point that must be borne in mind is that while abortion, the deliberate termination of a human pregnancy (most often performed during the first 28 weeks of pregnancy) is unavailable and indeed illegal in Malta, this does not prevent Maltese from travelling abroad in order to secure termination of pregnancy in significant numbers.[19] The Malta National Statistics Office stated in 2010 that "the past 10 years saw an average number of 57 abortions per year being carried out on Maltese nationals in England and Wales" alone.[20] Furthermore, tourists are often unaware that ECP is not available in Malta and may have few qualms to carry out an abortion in their own country. It is for this reason that FIGO also stated the obvious: "ECPs can prevent abortions by reducing unwanted pregnancies".[6]

All discussions on this topic should therefore be informed by, nay, predicated by the following six points:

1. There is no extant proof that ECP prevents implantation.
2. Locally available products can and are already being used as ECP.
3. There are websites that deliver the ECP door to door from overseas.
4. There is central European Union authorisation for a form of ECP –this ECP may be imported under current legislation.
5. Even Catholic Bishops have acknowledged that ECP does not prevent implantation. Naturally the Church only approves the use of ECP for rape.
6. ECP may *prevent* abortion by preventing unwanted pregnancies.

In conclusion, this particular media furore has once again highlighted the local penchant for generating storms in teacups, wasting time, effort and resources on a non-issue. Reservations dependent on science should be settled by scientific evidence. This particular topic has needlessly vexed individuals and groups into dogmatic postures that are entirely without basis in fact – they are fighting a lost battle.

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Cover Picture:
'Sailing'
By Bertha Darmanin

Bertha was born in 1954 and works within the Faculty of Health Sciences, University of Malta. She studied art privately with local artists and attended various courses set up by foreign artists. She participated in a number of collective exhibitions and her works may be found in both local and foreign locations. Her preferred medium is watercolour.

Original Article

Osteoporotic hip fractures – Three-year follow-up mortality rate in Malta

Stephan Grech, Sarah Cuschieri

Abstract

Introduction: Primary osteoporosis is a major factor in fragility hip fractures. The index fracture is loaded with morbidity and increased mortality in these very fragile patients. The aim of the study was to evaluate the mortality rate after 3 months, 1 year and 3 years post hip fracture with possible identification of any relationship between different hip fracture types and mortality.

Method: A retrospective analysis of all hip fracture patients admitted to Mater Dei Hospital, from January to December 2011 was performed. Data was gathered from the operating theatre notes, the patient archiving and communication system and the electronic case summary software. The mortality data was achieved from the National Mortality Registry. Statistical analysis was performed.

Results: Out of 281 patients with a hip fracture, 47% died (mortality group) within 3 years with a female predominance (68.9%). Within the mortality group, sustaining an intertrochanteric fracture exhibited a statistical difference between the females and males.

Within 90 days of a hip fracture, the mortality rate was of 12.8% with the majority of the patients sustaining an intertrochanteric. The median survival period following hip fractures was 190 days for subcapital, 297 days for intertrochanteric and 427 days for subtrochanteric fractures.

Conclusion: The mortality rate in our study compares well with the published results of similar studies. A team effort aimed at giving the best possible care and minimize the morbidity and mortality should be endeavored. This should encompass the whole pathway, starting with prevention and finishing with appropriate community care after hospital discharge.

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Keywords

Mortality; Osteoporosis; Femoral fractures; Osteoporotic fractures

Introduction

The elderly population stands a higher risk of sustaining hip fractures. The main factor is the establishment of osteoporosis, resulting in weaker bones.[1-2] Hip fractures have been directly linked to an increased risk for premature mortality rates, lasting over a long period of time following the actual fracture.[3] This increase in mortality rate has been found to be related to various complications directly related to the fracture itself or the result of the surgery and period of relative immobility. These include pulmonary embolism, pulmonary complications, urinary tract infections and heart failure.[2,4-5] The excess mortality can also be attributed to the various risk factors that predispose to frequent falls and sustaining hip fractures.[1,6]

The reported one-year mortality rate after sustaining a hip fracture is 14% to 58%; with a relative risk of 4% increase per year.[7-9] The first year following a hip fracture appears to be the most critical period regarding mortality. In the first 3 months post surgery, the death rate increases 8 fold for males and 5 fold for female patients, when compared to age and sex-matched controls.[10] The length of stay in hospital has also been associated with increased mortality. A hospital stay of between eleven and fourteen days was found to have an odd's of 32% for a patient to die within 30 days of the operation. The length of stay in hospital is directly proportional to the odd's increase.[11]

The aim of this study was to investigate the mortality rates at 3 months, 1 year and 3 years after sustaining an osteoporotic hip fracture. We also investigated any possible associations between the different fracture types and the mortality.

Method

An observational retrospective study was performed analyzing all emergency hip fractures requiring surgery, presenting to Mater Dei Hospital, Malta, between January to December 2011. With the permission of the Chairman of the Department of Trauma and Orthopaedics as well as the Central Performance Unit (CPU), the operated traumatic hip fractures list was obtained.

The inclusion criteria for our study were patients over 60 years of age suffering a hip fracture following a low energy injury. A low energy hip fracture was defined as a fracture suffered after minimal or no trauma. For the purpose of this study, these were considered to be osteoporotic in nature.[12] The mechanism of injury was determined by going over the admission notes from the A&E department. The exclusion criteria were those patients that were on long-term steroids, patients who consume large amounts of alcohol (over 3 units daily in males, over 2 units daily in females), had a history of malignancy, hyperthyroidism or were on warfarin as well as those sustaining a high-energy trauma.

Each osteoporotic patient was investigated with regards to the length of stay by using the 'Electronic case summary' software at Mater Dei Hospital. The picture archiving and communication system (PACS) was used to investigate whether each patient re-presented to a state health care institution with another osteoporotic fracture (defined as distal radius or vertebral fracture for the purpose of this study) over a period of 3 years following the primary hip fracture. Permissions from the hospital data protection office were obtained.

The survival rate from date of operation up till December 2014, was obtained from Malta National Mortality Registry, Directorate of the Health and Information and Research. Unfortunately the cause of death for these patients was not available. Therefore only the mortality rate could be established. The mortality rate in the first 90 days post-osteoporotic hip fracture was investigated as well as that after the first and third year post-surgery.

Data was stored in a spreadsheet and statistical analyses were performed using SPSS IBM v.11. The data was divided into 3 groups according to the 3 different types of osteoporotic hip fractures (subtrochanteric, subcapital, intertrochanteric) requiring different operative procedures. Each sub-group was subdivided according to the gender and the mean age and mean hospital stay for each subgroup.

Patients who passed away in the 3 year period post HIP FRACTURE, were labeled as "Mortality group" for easy referral in this paper. An independent t-test was performed to evaluate the mean gender age within the mortality group. Pearson chi-squared was used to evaluate the significance between gender and type of osteoporotic fractures while ANOVA was used for the mean hospital stay post-surgery. Kaplan-Meier survival analysis for the three different hip fractures was performed. A p-value of ≤ 0.05 was considered significant.

Results

In a three-year follow up of osteoporotic patients presenting to Mater Dei Hospital, Malta in 2011 with hip fractures patients (n=281), there were 131 who died by 2014 (the 'mortality group').

The mean age in the mortality group was 84.3 +/- 7.8 (2SD). The mean age in females was of 85.20 +/- 7 (2SD) and male mean age of 82.3 +/- 9 (2SD). A significant age difference between females and males was found (p=0.047) within the 'mortality group'. There was a significant difference in the mortality rate between males and females suffering an intertrochanteric fracture (Table 1)

There was no difference in the length of hospital stay (p=0.149) for the 'mortality group' between females and males (respectively 10 +/- 8.6 (2SD) days and 10 +/- 10.3 (2SD). Table 2. Shows the length of stay in hospital following different fractures, by gender.

Within 90 days of sustaining the osteoporotic hip fracture and undergoing the appropriate surgery, the mortality rate was of 12.8% (n=36). The majority of these patients (n=23) had sustained an intertrochanteric hip fracture and required a dynamic hip screw and plate. Figure 1 shows the different types of fractures and the percentage population death at 90 days.

Table 1: *Represents types of osteoporotic hip fracture frequency according to gender and mean age within the 'mortality group'*

Type of fracture	Gender	Number of people (%)	Mean age in years (SD)	p- value*
Intertrochanteric	Females	58 (44.3)	87.10 (5.6)	0.014
	Males	25 (19.1)	82.84 (9.8)	
Subcapital	Females	24 (18.3)	81.46 (8.6)	0.937
	Males	13 (9.9)	81.23 (7.8)	
Subtrochanteric	Females	9 (6.9)	82.89 (6.8)	0.878
	Males	2 (1.5)	82 (9.9)	

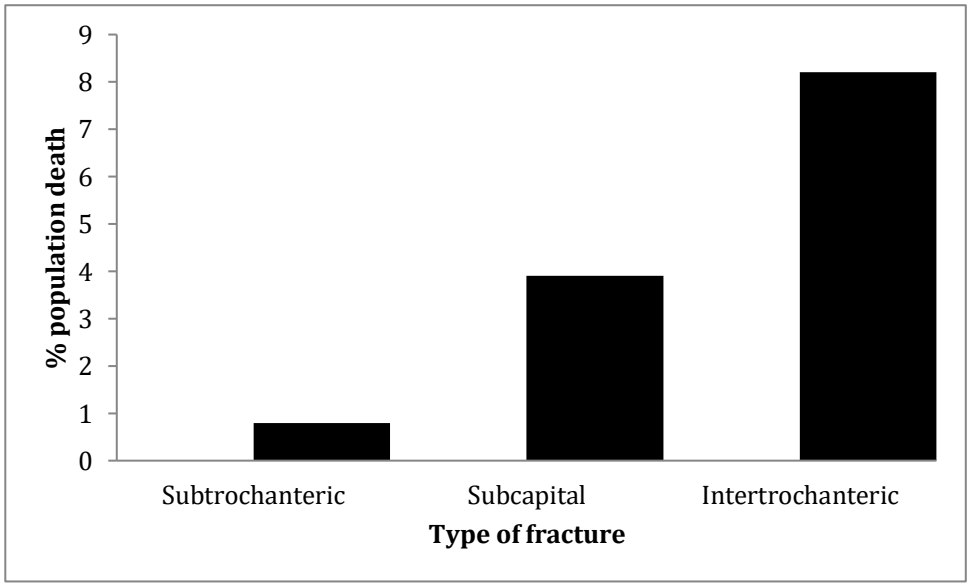
* Shows the significance between mean age and gender according to different types of fractures

Table 2: *Illustrate the length of stay in hospital following different fractures, by gender*

Type of fracture	Gender (N^{o})	Mean length of stay (SD)	p- value*
Intertrochanteric	Females (58)	9.71 (7.1)	0.078
	Males (25)	10.20 (9.9)	
Subcapital	Females (24)	9.75 (9.2)	0.284
	Males (13)	10.00 (12)	
Subtrochanteric	Females (9)	12.44 (15.3)	0.446
	Males (2)	11.00 (2.8)	

* Shows the significance between mean hospital stay and gender according to different types of fractures

Figure 1*: Mortality rate sustained within 90 days according to different osteoporotic hip fracture*

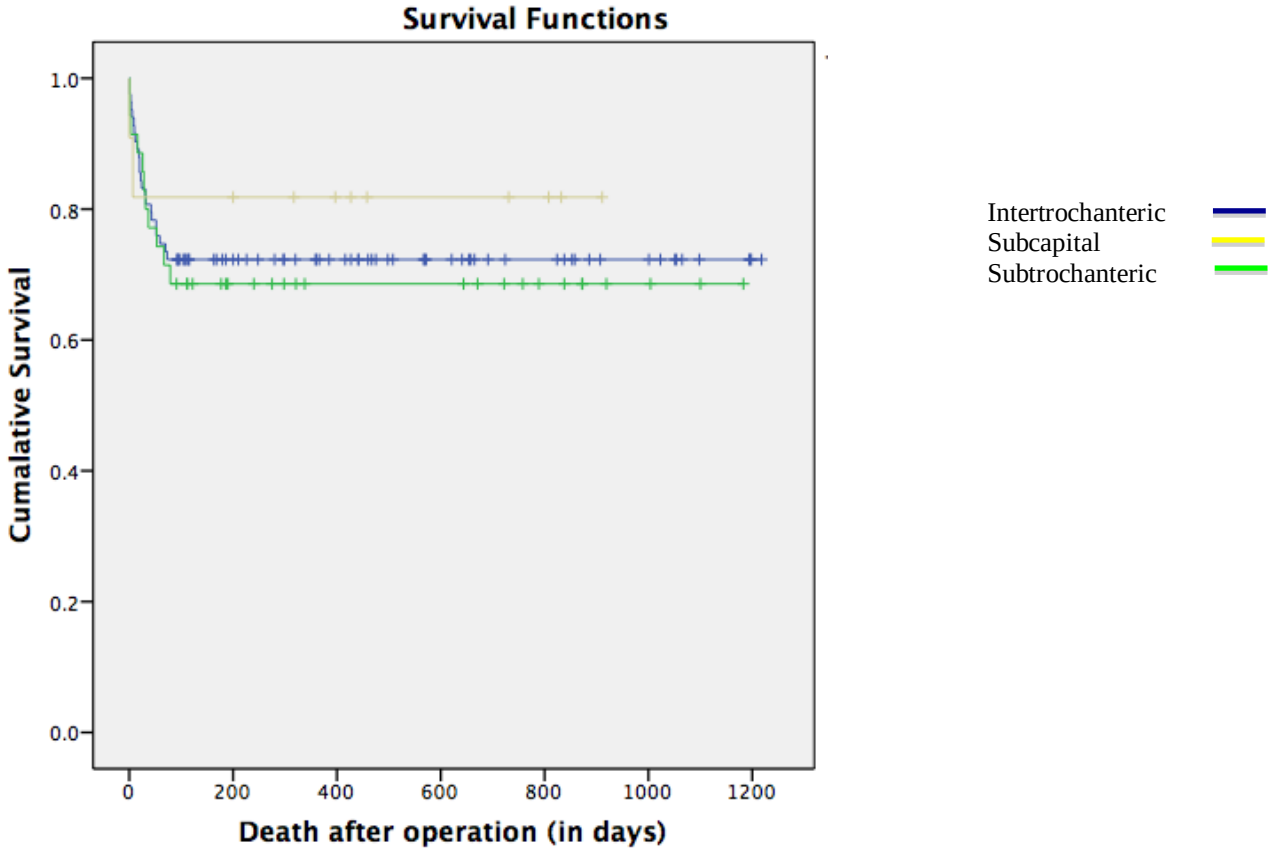


There was no significant difference between the different types of fractures and mortality rate in the first 3 months post osteoporotic fracture (p=0.775), nor was significance found between gender and a previous diagnosis of diabetes mellitus and mortality rate after 90 days of osteoporotic hip fracture (p=0.377; p=0.195 respectively). On evaluating further this 3-months mortality group and taking in consideration that the mean hospital stay for hip fractures in Malta is of 11 days, the mortality of hospital in-patient rate was established.[15] An in-hospital mortality rate of 4.6% (n=13) was established with a female predominance (n=9) and a mean age of 85.7 (7.8 SD), with no statistical significance between the type of fracture and age (p=0.509).

The mortality rate in the first year after the osteoporotic hip fracture was 25.6% (n=72) out of which 2 patients sustained another fracture and died within year one. During the first year after the index hip fracture, there were 8 patients who sustained another fragility fracture. The majority of patients suffering a second or more fragility fracture were females.

The median survival after an intertrochanteric hip fracture was of 297 days; subcapital fracture of 190 days and subtrochanteric fracture of 427 days. (Figure 2)

Figure 2: *Kaplan-Meier survival analysis of the three different hip fractures*



After three years follow-up the majority of patients who died had undergone a dynamic hip screw surgery due to an intratrochanteric fracture (n=83) with the majority being female (n=58). Within this subgroup, there were 4 patients who sustained a re-fracture before dying with one patient sustaining a second fracture and dying within 1 month. A single patient passed away 3 months after suffering the second fracture.

Females sustaining a hemiarthroplasty due to a subcapital fracture showed the highest mortality rate within this group (n=24). Out of all the subcapital fracture mortaltiy population (n=37), there were 4 patients who sustained a re-fracture prior to dying. Two of these died within a month after the second fracture.

Those sustaining a subtrochanteric fracture had the lowest mortality rate (n=11) and from this sub-

population there were no re-fractures prior to their death.

Discussion

Hip fractures can be subdivided into 3 (intertrochanteric, subtrochanteric and subcapital), depending on the location of the fracture within the proximal femur. Intertrochanteric fractures lie along a line between the greater and the lesser trochanter on the femur.[13]. These are extra capsular fractures where the blood supply to the femur is usually preserved, making them amenable to osteosynthesis using a dynamic hip screw and plate construct. Subcapital fractures are intracapsular fractures. The blood supply is usually interrupted leading to a very high risk of avascular necrosis of the femoral head, which is why replacing the proximal femur is usually indicated. Subtrochanteric fractures lie below the level of the trochanters, blood supply is usually sufficient to allow oateosyntehsis. The majority of the study's population had an intertrochanteric fracture. In fact significance was found between the mortality population under study and this type of fracture. The mean survival for the intertrochanteric fracture was of 297 days even though the majority of the population dying after 3 years had sustained an initial intertrochanteric fracture.

It has been well established that the most critical period for those with an osteoporotic hip fracture to die is the first 3 months of the injury.[10] In Malta, when compared to other countries, there appears to be a low mortality rate for this critical period of 12.8%.[14] Interestingly to notice is that the majority of these had sustained an intertrochanteric fracture although no statistical significance was found for this observation at 3 months following the injury.

The one-year all cause mortality was of 25.6% for the osteoporotic hip fractures study population, which is in keeping with other studies 24.5% 1-year mortality rates.[16-17] When considering our mortality rate with the total deaths of the Maltese residents in 2011, the hip fracture mortality rate made up 2.2% of the total Maltese mortality rate for the same year.[18] On comparing the 2011 total Maltese Islands population mortality age groups to the study's one-year mortality group mean age (84 years), it was noticed, that it formed part of the largest mortality age group for the year.

The three-year all cause mortality rate of patients sustaining hip fractures in 2011 was of 46.6%, showing a significant difference between genders. The mean age for this "mortality" population was of 84 years, which is in keeping with other studies.[1-2]

Once a hip fracture has been sustained, the patient is at risk not only of undergoing a metabolic complication, which potentially results in death, but also a further fracture. These fractures are a common occurrence and these continue to hinder the morbidity and increase the mortality of the patient.[15] Within the 1-year mortality group, 11% of these had a second or more osteoporotic fractures before dying.

The mortality burden following hip fractures is as expected within elderly population especially due to higher risks of re-fractures and complications. This burden can be improved with bisphosphonates being prescribed to all osteoporotic hip fracture patients to try to reduce the risk of re-fractures.[15] Also, with the introduction of the orthogeriatric services in Malta, and therefore better structures care for the elderly with fragile fracture, the mortality rate should be improved. This service already appears to have improved the mortality rates when compared to other European countries even though Maltese patients tend to be frailer.[19]

Study limitations

Although the study takes into account the total hip fractures presenting to Mater Dei Hospital in a year, the number analyzed is still relatively small. Further research with possible larger patient cohort and longer observation period is suggested.

Conclusion

The mortality rate following an osteoporotic hip fractures mostly affect the Maltese female population. Those sustained an intertrochanteric fracture appears to be mostly at risk to die even though a subcapital fracture has the lowest median survival rates. Overall, the Maltese one–year all cause mortality appears to be better than other countries. With further mortality improvements with prevention of re-fractures and specialized care for these frail elderly, the mortality rate due to hip fractures is expected to improve.

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Original Article

Free access to drinking water in schools: Development of a survey tool

Michelle Deguara, Charmaine Gauci

Abstract

Introduction: Water is important for many physiological functions in the human body and contains no calories, making it the ideal source of hydration and an imperative alternative to Sugar Sweetened Beverages (SSBs). The consumption of SSBs is identified as a risk factor for weight problems in children (overweight and obesity) and is also linked to the development of type 2 diabetes.[1] Targeting schools to increase consumption of water can have an effect on the consumption of SSBs.[2]

Method: A literature search was done in Google Scholar, PubMed and HyDi database for a survey tool which assesses the provision of drinking water that was already validated and piloted. Three studies were found relevant for this purpose. A draft tool was produced and was then validated using face validation and also piloted in four schools to produce the final survey tool which is quantitative in nature.

Conclusion: The survey tool that was developed and piloted in this study can be used to assess the provision of drinking water across Maltese schools.

Keywords

Drinking water, Sugar sweetened beverages, Schools, Survey tool

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Introduction

Water is an essential nutrient important for many physiological and cognitive functions of the human body (Table 1).[1,3–5] Children lose water at a faster rate when compared to adults and dehydration sets in faster in children who are exposed to warm temperatures especially in summer and during physical activity. The thirst response is less well-developed in children therefore they might not feel the need to drink when they start to get dehydrated.[3] If children are not reminded to drink adequate volumes of water frequently (Table 2), they might spend hours during the day without consuming any water.[4] When children feel thirsty, their cognitive functions and level of concentration would have already diminished by 10 per cent, and these functions continue to deteriorate with increasing levels of dehydration. Some of the signs and symptoms of dehydration may include: lethargy, thirst, headache, light-headedness, irritability, lack of concentration, concentrated urine, constipation and bed wetting.[3]

In the current global epidemic of childhood obesity water offers multiple benefits and contains no calories, making it the ideal source of hydration and an imperative alternative to SSBs. The consumption of SSBs is identified as a risk factor of weight problems in children (overweight and obesity) and is also linked to the development of Type 2 diabetes.[1] In Malta, soft drinks and other SSBs are prohibited beverages in schools and students are also not allowed to bring such beverages from home.[6-7] Decreasing the availability of SSBs and keeping well hydrated with water decreases the consumption of SSBs and in turn decreases a number of health problems in children.[2] Literature suggests that increasing daily water intake to approximately 1 litre, no consumption of SSBs and engaging in daily low to moderate intensity physical activity are key factors in weight management especially of overweight and obese children.[8]

Table 1: *A list of the benefits of drinking an adequate daily volume of water*

The benefits of drinking water:

- Maintenance of renal function
- Maintenance of blood volume
- Helps in keeping a healthy weight
- Weight reduction for overweight or obese children
- Protection of health and well-being
- Regulation and maintenance of body temperature
- Improvement in cognition and ability to learn
- Improvement in the level of concentration during lessons
- Enablement of good behaviour and a decrease of restlessness in the classroom
- Improvement in performance during sports
- Improvement in strength and endurance during physical activity
- Decrease in dental carries

Table 2: *Recommended Daily Intake of Water (The British Dietetic Association, 2013)*

Age	**Adequate water intake (ml/day)**
1-2 years	880-960
2-3 years	1040
4-8 years	1280
9-13 years	Boys 1680 Girls 1520
Children over 14 years	Boys 2000 Girls 1600

Children spend most of their waking hours in school, making schools the ideal environment to promote healthy lifestyle choices, one of which is the drinking of water instead of SSBs. Schools can also target health promotion messages to children of different ethnicities and socioeconomic backgrounds.[5,9] To increase the level of water consumption, teachers should encourage children to carry water bottles with them during physical activity, to drink water before, during and after exercises and there should also be regular drinking reminders during the lessons.[3] Health promotion campaigns against childhood obesity should take a holistic approach by focusing the campaign on schools while also addressing other important environments such as the family and the community

the child is living in.[5,9]

In a study conducted by Loughridge and Barrat, the researchers compared the effectiveness of two different programs aimed at increasing the consumption of water in British Secondary schools. One program improved the access to water only, while the other program improved the access to drinking water coupled with promotional activities. The latter program resulted in increased water consumption and better outcomes.[10] Similar results were also found in two other studies by Patel *et al* and Muckelbauer *et al.*[11,12]

Recent research suggests that when SSBs are available in schools, consumption of these beverages increases which in turn leads to an increase in the daily calorie intake and hence obesity [5]. Actions that can help in reducing SSBs' consumption in children include:

- Limiting the marketing and publicity of SSBs which targets children;
- Reducing the availability and access to SSBs in school
- Introducing taxation on SSBs [1]

In Malta, the 'Whole School Approach to a Healthy Lifestyle: Healthy Eating and Physical Activity' policy (2015), outlined that all schools should have an adequate number of water outlets and should also have free access to clean drinking water which is sited strictly outside toilet areas.[6] In 2011, the National Audit Office audited the provision of water in schools. 80 Head of Schools from the 121 Heads that answered to this audit claimed that the school needed to have better provision of free drinking water.[13]

In order to plan for the provision of free access to water in schools, the current situation needs to be mapped out. The aim of this study was to create a validated survey tool which can be used to assess the provision of drinking water in Maltese schools hence providing baseline information which can be used during the development of a plan for the supply of water in all schools.

Methodology

A literature search was done for a similar tool which was validated and piloted, in Google Scholar, PubMed and HyDi database. Three studies (Center For Disease Control (CDC), 2011; Education and Resources for Improving Childhood Continence, 2006; National Audit Office, 2011) were found to be relevant for this purpose. The main tool that was chosen was the one used in a performance audit, 'Achieving a Healthier Nutrition Environment in Schools', conducted by the National Audit Office (NAO) in 2011. This tool was found to be the most appropriate tool to collect the information needed and it was already validated, piloted and used for the local population.

Stem questions and stem options that were thought to be irrelevant were removed from the original tool, while other questions were added to the NAO tool from the other two studies mentioned above. This produced a survey tool in the form of a quantitative questionnaire which was validated using a face validation method. The tool was discussed with the Director of Health Promotion and Disease Prevention within the Ministry of Health, with the Head Project Team Education and with the Director of School Resources Management within the Ministry of Education and Employment. Questions were assessed whether they were clear, comprehensible and if they were an adequate measure to collect specific information. The suggestions that came up during these discussions were used to further amend the tool.

The tool was then piloted in four schools (Primary A, Primary B, Middle School and a Secondary School). The questionnaire was sent to the Heads of School via email and when it was answered it was sent back also by email. Each Head of School was then contacted to obtain feedback on the construct of the tool, any ambiguous questions and any information that should have been added to the tool. The tool was adapted to include this feedback and the final version of the tool was produced.

Discussion and Implementation

The level of water consumption among children and adolescents in schools depends on different variables including the number of water outlets available, the location of these outlets and how much these outlets attract the interest of students.[4] It is important to have a written policy on the implementation of free access to water in the school. For such policies to be effective, the policy should include ways of increasing access to water and also methods to educate and promote the consumption of water among students, staff and parents.[5]

In water programs where children are

expected to fill their personal water bottles, the bottles must be transparent so that their contents can be viewed and storage for the labelled water bottles is to be provided by the school.[12] In studies where storage for the water bottles was not provided, some of the children either lost their bottles or left them at home. Therefore when storage is not available, paper cups or replacement bottles should be supplied for those that forget their filling vessel.[10,11] Another important factor that should be kept in mind is frequent toilet breaks for children and the provision of a clean toilet environment. Children who have restricted access to toilets will not increase their consumption of water in order to avoid frequent visits to the toilet.[4]

Steps to be considered when implementing a Water Access Program (adapted from Grummon *et al*[14] and Centre for Disease Control[15])

I. ***Build your team and gather support***

Important stakeholders should be identified and involved in regular meetings to make the program successful. Teachers should act as role models by promoting consumption of water and drinking fresh water themselves while parents should help in maintaining the healthy beverage choices at home too.[14]

II. ***Assess the school environment***

Schools need to be assessed for current practices regarding the provision of free access to water. This can be done by using the validated tool developed through this study, which can gather the relevant information and highlight areas which need improvement during the implementation process.[14]

III. ***Secure the provision of safe and appealing water***

The locations where water outlets are to be sited and the water delivery method should be decided at the beginning of the program as these decisions will influence future structural decisions, maintenance and funding of the program. The water program should also include methods of how water quality from these outlets is to be tested and how frequently.[14,15]

IV. ***Strengthen and Sustain the Water Program***

The Water Program should be outlined clearly and ideally written as a school policy so that it remains sustainable despite any changes in the Head of school or any other members of staff.[14] As already mentioned increasing or improving access to free water is strengthened and made more effective when it is combined with educational and promotional activities.[14,15] Promotion of the benefits of water should be placed close to water outlets to make them more attractive and promotional messages should be included in lesson plans in the form of interactive activities (videos, acting, drawing competitions) and also sent to parents (e.g. in a newsletter).[15]

V. ***Monitor and Evaluate the Program***

Every program should have a plan on how to evaluate different stages of the implementation and success of the program. A needs assessment should be done at the beginning of the implementation to outline the gaps between the current program, if in place, and the desired endpoint for the new program. Process evaluation helps in finding any pitfalls in the current program which can be worked upon to improve its effectiveness. After the program has been implemented and running for some time outcome evaluation should occur to analyse whether the objectives of the program have been met or not. Important objectives of implementing free access to water for students are: increase in the daily consumption of water, decrease in the daily consumption of SSBs, changes in the knowledge and attitudes on the health benefits of consuming water. Outcome evaluation can generate results which are then used to highlight the improvements in knowledge, attitudes and practices and also to secure funding.[14,15]

Conclusion

This study highlights the importance of increasing the consumption of water in schools in order to gain the full benefits of drinking water. This information is to be used when discussing the need of implementing free access to water in schools with the relevant stakeholders. When implementing a free water access program, a feasibility study which assesses the environment in schools must be conducted. The validated survey tool that was developed through this study can be used to assess the provision of drinking water in all public, private and church schools to obtain a better picture of what is happening across the Maltese educational system; an important step in the implementation process.

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Original Article

Adverse events following intravesical Bacillus Calmette-Guérin therapy in Mater Dei Hospital, Malta

Gerald Busuttil, Luke Zammit, Christine Debattista

Abstract

Introduction: Intravesical administration of Bacillus Calmette-Guerin (BCG), following transurethral resection of bladder tumour, has been shown to reduce recurrence and progression in appropriately selected patients with non-muscle invasive bladder cancer. The aim of the study was to report the local incidence and range of adverse events experienced by patients managed with intravesical BCG.

Methods**:** All patients who received at least one dose of intravesical BCG treatment at Mater Dei Hospital in 2014 were included in the study. A database including demographic, histological and chronological data, together with complication type, degree and treatment required was created. Patient medical files were reviewed and the patients were invited to take part in this audit via a telephone survey

Results: 55 patients satisfied inclusion criteria and were included in the study. 54 patients were documented to have had induction BCG, with maintenance BCG in 32 patients. 22 of these experienced at least 1 adverse event with BCG, whilst 33 had no complications. 1 patient had 3 adverse events, 7 patients had 2 adverse events and 14 patients had 1 complication. Most adverse events were considered to be mild or moderate in severity. Storage bladder symptoms accounted for most of these adverse events. No death as a consequence of intravesical BCG therapy was recorded.

Conclusion: Intravesical BCG therapy remains one of the mainstay therapies in the management of bladder cancer. The majority of adverse effects recorded were self-limiting or easily treatable with oral analgesics or antibiotics.

Keywords

Bladder cancer, Intravesical Bacillus Calmette Guerin, Morbidity.

Introduction

Transitional cell cancer of the urinary bladder remains a common disease in the western world despite reduction in smoking habits and legislation which has banned carcinogenic industrial substances associated with bladder cancer causation. Urothelial bladder cancer is the 7th most common cancer diagnosis in males and 17th in females world-wide, with a higher incidence in the developed world.[1]

At initial presentation, three fourths of bladder tumours are non-muscle invasive, this group of bladder cancers represent a diverse group of tumours with a wide spectrum in their potential for recurrence, progression and eventual adverse outcomes.[2] The wide variation in the one-year recurrence rate quoted in the literature after initial trans-urethral resection, ranging from 15 to 61% attests to the heterogeneous character of non-muscle

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invasive bladder cancer (NMIBC).[3]

The European Organisation for Research and Treatment of Cancer (EORTC) has developed tables which stratify NMIBC cases into risk categories based on number of tumours, tumour size, T stage, grade, recurrence history and presence of carcinoma in situ. These tables have been externally validated, and are extensively used to guide treatment and follow up.[4- 5]

The mainstay of treatment in NMIBC remains a good quality endoscopic resection, with second re-staging resection in selected cases and various regimens of intravesical chemotherapy or immunotherapy.[6] Intravesical immunotherapy is also the primary treatment for isolated carcinoma in situ of the urinary tract.

Maintenance immunotherapy with Bacillus Calmette Guerin (BCG) is the only intravesical therapy which has been shown to reduce both recurrence and progression rates in NMIBC, however its use is reserved to EORTC intermediate and high risk categories in view of its higher morbidity compared to intravesical chemotherapy regimens.[7- 8]

Method

A retrospective list of patients who received at least one dose of intravesical BCG for the treatment of non-muscle invasive bladder cancer at Mater Dei Hospital in 2014 where included. Index patient list was compiled using clinical departmental database which is used to register and follow up all patients undergoing intravesical BCG therapy.

All the patients in our cohort received BCG OncoTice® strain (MSD Sharp & Dohme GMBH). Intravesical BCG instillation follows the Evidence-based Guidelines for Best Practice in Urological Health Care published by the European Association of Urology Nurses.[9]

One phial 12.5mg per vial containing 2-8 x 10^8 CFU Tice BCG is diluted in 60 mls of sterile 0.9% saline solution and instilled in the bladder via a 10 or 12F bladder catheter using aseptic technique and strict infection control measures.

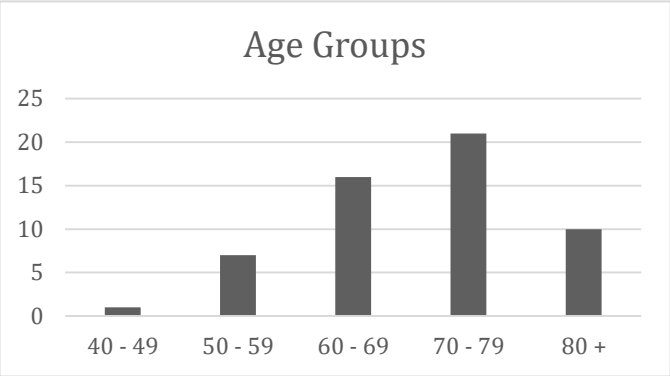
Induction intravesical BCG protocol involves six instillations one week apart, starting not less than two weeks after initial diagnostic TURBT, with a maintenance protocol consisting of three doses of intravesical BCG a week apart at three monthly intervals over three years in high risk cases of non-muscle invasive bladder cancer.

A custom designed database was written to include demographic, histological and chronological data, together with complication type, degree and treatment. Data sources included medical case notes, departmental intravesical treatment patient database and a standard telephone survey one week after each BCG dose.

Results

55 patients where included in the study, all of which received at least one dose of intravesical BCG in 2014. 46 of these were male and only 9 being female. Most of these patients where elderly, as show in Figure 1.

***Figure 1**: Patient age demographics*



The indications for BCG treatment included various subgroups of high risk or recurrent non-muscle invasive bladder cancer, as showing in Table 1. The indication for BCG treatment was not documented in one patient. 54 patients received induction BCG, 32 of these went on to received maintenance BCG.

***Table 1:** Tumour characteristics in patients undergoing BCG therapy*

Indication	
recurrent T1G3 TCC	15
solitary T1 TCC	9
multifocal T1 TCC	9
recurrent T1 TCC	9
solitary T1 G3 TCC	4
multifocal G3 TCC	3
multifocal T1G3 TCC	3
recurrent CIS	1
Not available	1

22 patients out of 55 experienced at least one adverse event with BCG. One patient had three adverse events, seven patients had 2 adverse events, 14 patients had one complication. Most of these adverse events were considered to be of mild or moderate in severity, with two events qualifying as serious adverse event (SAE) by American Food and Drug Administration criteria (culture positive UTI requiring admission for intravenous antibiotics). All other adverse events were either managed conservatively or else with simple measures such as analgesics, oral antibiotics or delay in the next dose of BCG with a good outcome in all cases. No cases of mortality from intravesical BCG therapy were recorded. The full list of adverse events reported is given in Figure 2. Figure 3 outlines the treatment administered to manage these complications.

***Figure 2**: List of adverse events reported in BCG treated patients*

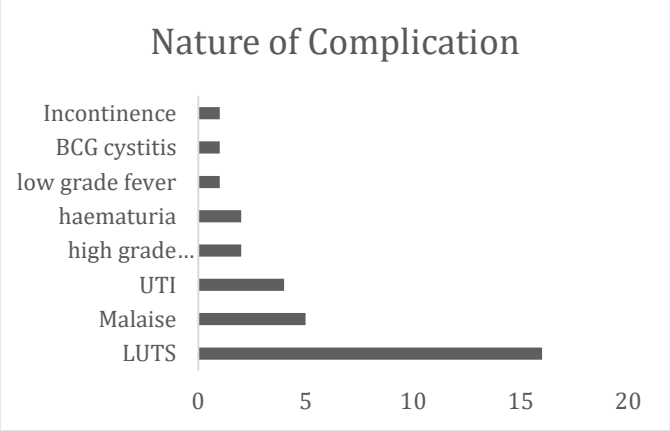
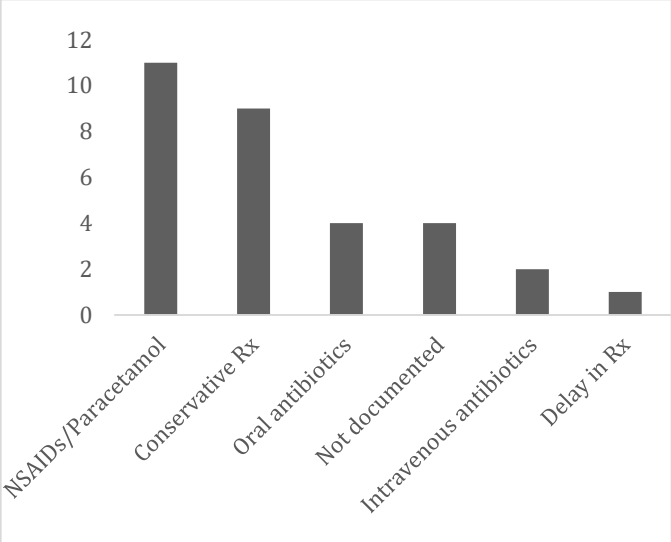


***Figure 3:** Treatment strategies adopted to manage adverse events secondary to intravesical BCG therapy*



Discussion

Intravesical Bacillus Calmette-Guérin, an attenuated form of the *Mycobacterium bovis*, has been used by urologists for many years following first reports of its potential anti-carcinogenic effects in 1929 by Pearl.[10] In an autopsy series he noticed that cancer occurred less frequently in individuals with active tuberculous lesions compared to healthy controls, and postulated that tuberculous infection may be protective in this respect. Morales *et al* were the first to describe intravesical BCG use for the treatment of bladder cancer in in 1976, where they showed a significantly reduced recurrence rate in nine treated patients. The regimen used, consisting of six weekly intravesical instillations of BCG, is still the most popular induction protocol in most centres.[11]

Further investigation in the optimal BCG schedule, published by Lamm *et al* in 2000, which showed that progression rates can be reduced by an additional maintenance protocol has resulted in the widespread adoption of this combined induction-maintenance schedule for the treatment of high-risk non-muscle invasive bladder cancer following initial diagnosis at transurethral resection.[12]

Risk stratification in this patient group is essential for many reasons. Non-muscle invasive bladder cancer included a heterogeneous cohort of patients with very variable cancer specific mortality outcomes. Intravesical BCG therapy has a significant morbidity, with a potential for serious adverse events, treating low risk patients with intravesical BCG has the potential for overtreatment and unnecessary morbidity. In view of this the European Organization for the Treatment and Research of Cancer (EORTC) has published risk stratification nomograms which are used to guide patient selection after histopathological diagnosis of NMIBC.[13]

In this retrospective study the local morbidity from intravesical BCG therapy was assessed and compared to similar series. 40% of the patients included reported at least one adverse event, which is within the published rate of 10-50% in other series.[14-16]

Half of the adverse events were reported as irritative culture-negative lower urinary tract symptoms, this is not surprising and is in keeping with the inflammatory bladder reaction which invariably follows intravesical BCG instillation. Other common reactions included culture positive

UTI and haematuria. Uncommon effects were mostly systemic in nature, including malaise and fever. This highlights the fact that the adverse effect profile of intravesical BCG extends beyond the confines of the lower urinary tract, and should be considered as a therapeutic modality with potential for severe systemic side effects, including potentially life threatening BCG sepsis.

This study has some strengths and numerous limitations. The index case list captures all the patients treated with intravesical BCG for the given study period at a national level as this therapy is administered by one urology unit and a clinical database is in place to register and follow up all patients receiving BCG treatment. This also allows for standardisation of the BCG strain, dose and method of administration across the patient cohort.

The limitations of this study are mostly related to its retrospective nature, which may have resulted in incomplete data capture and underestimation of adverse events rates. In addition, patients may have presented to their private general practitioner or government health centre with minor BCG-therapy related complaints, and these events may have gone unnoticed and unreported by the investigators. In an attempt to limit these unreported adverse events all patients where contacted by phone a week after their BCG dose and the severity of any events were also assessed at this time. Moreover, in the absence of strict definitions of drug related adverse events severity, the classification of adverse events into mild or moderate is somewhat arbitrary. The FDA definition of a serious event was used to identify serious morbidity according to established criteria.

The relatively low number of patients on maintenance intravesical BCG may also have had an impact on morbidity rates. This is a matter of debate in the urological community as maintenance BCG treatment has not been shown to increase morbidity in published literature. However, this does highlight the clinical concern that maintenance BCG might be underutilised in our unit, especially given that most of the patients in this patient cohort classify as EORTC high-risk patients.

Conclusions

Morbidity secondary to intravesical BCG therapy in the local population of high-risk non-muscle invasive bladder cancer patients compares favourably to published series. Adverse events are mostly low grade and are managed successfully with simple measures in the majority of cases.

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Original Article

Social Interaction of Cancer Survivors in Malta. A sociological analysis

Michael Briguglio, Charon Tedesco

Abstract:

This research analyzes social interaction of cancer patients in Malta. In particular it applies a qualitative sociological approach to verify how cancer patients interact with family members and society. The research concludes that social interaction of cancer survivors in Malta is characterized by mixed experiences, but at the same time, all cancer patients emphasize the importance of family support. A major finding is that cancer patients do not simply receive support from family members, but also provide it themselves to their relatives. This is not an intended effect of cancer survivorship, but nevertheless it helps strengthen social bonds within families of cancer patients.

Keywords:

Cancer, sociological factors, social networks, social capital.

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Introduction

This research analyzes social interaction of cancer patients in Malta. In particular it applies a qualitative sociological approach to verify how cancer patients interact with family members and society.

This study was inspired by three main motives. First, one of the authors experienced cancer in her family and was prompted to analyze the challenges and interpretations of cancer patients sociologically. Second, this study aims to explore whether cancer patients relate to their illness in a fatalistic manner, or whether they give more importance to survival. Third, this study aims to raise awareness in academic and policy fields on the social dimension of cancer.

Cancer in Malta

Every year, in Malta, around 1,400 people develop Cancer, eventually resulting in the death of around one in every four.[1]

A Eurostat report published early in 2016 showed that in 2013 Malta had the highest shares of female deaths due to breast cancer in Europe, together with Cyprus. This was the cause of 21 per cent of deaths due to cancer among women in the two island states. The EU rate was 16 per cent. On the other hand, Malta had the lowest percentage of prostate cancer rates in the European Union, together with Italy, Luxembourg, Poland and Slovenia. The 8 per cent rate was lower that the EU rate of 10 per cent. The report also highlighted that lung cancer was the most prevalent fatal form of cancer in the EU and then men were more likely to be killed by cancer then women.[2]

At the same time, according to EUROCARE-4,[3] cancer survivorship in Malta is increasing. This includes survival rate in the two most common cancers among females and males respectively, namely breast cancer and prostate cancer. However, compared to the European rates of Cancer survivors, Malta still has lower rates of Cancer survivors than that of the European

average.[4]

Of direct relevance to this study, Malta's National Cancer Plan (2011-2015) refers to the patients' perceptions on Cancer. In its words:

> "A diagnosis of Cancer brings about a great deal of psychological distress in patients and their loved ones. This includes an increased uncertainty about the future, emotional instability, increased dependence on others, reduction of self-esteem and the perceived threat of possible death. Such distress puts Cancer patients at increased risk of developing psychological disorders".[5]

Within the context of Maltese society, a small-island state with a relatively high degree of family proximity (for example, through quasi-modified extended families and the coexistence of modern and traditional values),[6] social solidarity,[7] altruism,[8] and a hybrid welfare state,[9] it is of sociological relevance to verify whether social bonds of cancer patients are enabling them to cope with their experiences.

This specific dimension of cancer is under-researched in Malta. Apart from the undergraduate dissertation by Charon Tedesco[10], which provides empirical data for this article, other studies in the field deal with men's experience of their partners' breast cancer experiences[11], social work with family members of children with cancer[12] and with carers of terminally ill patients[13], young people and parental cancer[14], awareness, education and prevention of cancer for women[15] and for women with disability[16], and breast cancer and women with disability.[17] A common thread among these studies is the emphasis on the need for professional psychosocial services for persons in such situations.

Social aspects of illness

Caplan claims that social support is fundamental in helping patients with a chronic illness to adjust to their new situation.

> "Social support can exert major influence on a client's ability to cope with a chronic illness. An individual's coping responses during crises are influenced not only by his or her ego strength, but also by the quality of service and emotional support provided by the social network".[18]

Parsons regards illness as a legitimate type of deviance, as "the sick person is not regarded as responsible for his condition, he can't help it".[19] This argument is debatable in a welfare context where citizens are held increasingly responsible for their life-choices, but nevertheless health systems such as Malta's provide universal assistance to cancer sufferers. Parsons adds that the sick person is free from normal social responsibilities and has the right to be taken care of.

Along the same lines of Parsons, Bury says that persons experiencing chronic illness are largely dependent on others, and that this can disrupt their mutual give-and-take relationship, as the chronically ill person is unable to assist those helping him. Hence chronic illness is seen as a "disruptive force",[20] and sufferers tend to withdraw from normal social interactions.

Goffman says that persons will illness might be concerned with the possible experience of social stigma. In this case, they might hide their illness, especially if it is not physically visible, thus giving the impression that they are 'normal'. This social technique is referred to as 'passing'.[21]

Such situations may be stressful, where such individuals "must necessarily pay a great psychological price, a very high level of anxiety, in living a life that can be collapsed at any moment".[22]

If cancer is present on a visible part of the body such as the skin, sufferers might find it more difficult to conceal their situation. In such as case, the sufferer might possess "stigma, an undesired differentness from what we had anticipated".[23]

Stigma might also take place when sufferers cannot carry on their everyday life. They might be labelled as helpless individuals. Yet,

> "The stigmatised individual tends to hold the same beliefs about identity that we do; this is a pivotal fact. His deepest feelings about what he is may be his sense of being a 'normal', a human being like anyone else, a person, therefore, who deserves a fair chance and a fair break".[24]

In some cases, stigmatised persons may try to 'fix' the cause of their stigma.[25] For example, in the case of breast cancer, women might undergo mastectomy and subsequent breast reconstruction.

A more positive outlook on social aspects of illness has been provided by Putnam.[26] His social

capital theory focuses on the positive contribution of social cohesion, reciprocity, trust and similar social factors. As regards health, Putnam argues that social networks can provide material assistance and consequently reduce stress, they can reinforce norms of healthy lifestyles, they can help advocate better medical services and can help stimulate the body's immune system.[27]

Some empirical sociological research on cancer survivorship deals with concepts such as social networks and stigma respectively. For example Norberg et al[28] carried out a follow-up study on female breast cancer survivors 5 to 7 years after being operated upon. Some themes that emerged from discourses among survivors were the importance of social networks, the perceived importance of women's caring roles and other gendered differences. Positive thinking and being physically active were also emphasised as examples of individual responsibility.

Martinez-Ramos et al[29] found that female cancer survivors feared being stigmatized if they talked in public about their experiences, and that their female identities might be perceived negatively. They also emphasized the importance of social networks with families and communities, for example in social support and provision of care. Respondents also viewed advocacy of their experiences as important to help empower cancer survivors.

Kaiser[30] discovered different, and at times conflicting, interpretations of the term 'survivorship' among women who experienced breast cancer. These varied from feelings of alienation due to fear of recurrence of cancer to wishes to keep one's experience private.

Methodology

As stated above this study attempts to analyse social and family support of cancer patients in Malta. In order to answer this question, a qualitative-interpretative approach was used in order to enable respondents to open up on their life experiences.

For this purpose, semi-structured face-to-face interviews were carried by one of the authors of this article, Charon Tedesco, with 11 former cancer patients who were identified by a general practitioner, with the approval of the University of Malta Research Ethics Committee (UREC).

Respondents included three males and eight females, who gave their informed consent to being interviewed at their respective homes, on condition of anonymity. The following table explains in more detail:

Table 1: *Respondents' social background and type of cancer*

Fictitious name of Interviewee	Gender	Age when Diagnosed with Cancer	Type of Cancer	Cancer stage	Occupation
Manuel Falzon	Male	59	Large intestine Cancer	Stage 3	Construction
Noreen Galea	Female	43	Breast Cancer	Stage 3	Housewife
Mandy Cauchi	Female	40	Breast Cancer	Early stage	Housewife
Claudia Bugeja	Female	40	Breast Cancer	Advanced stage	Housewife
Rose Tanti	Female	38	Bowel Cancer	Malignant stage One	Businesswoman
Karen Mifsud	Female	45	Breast Cancer	Early stage	Housewife
Ramona Dalli	Female	53	Thyroid Cancer	Early stage	Housewife
Natasha Vassallo	Female	45	Uterus Cancer	Stage 3	Housewife
Nadine Borg	Female	44	Thyroid Cancer	Early stage	Housewife
Joe Borg	Male	65	Prostate Cancer	Early stage	Pensioner
Craig Thomas	Male	58	Skin Cancer	Early stage	Construction

It has to be emphasized that the qualitative methodology of this study precluded representative sampling. What this study provides is an in-depth study of the experiences and narratives of a convenience sample of cancer survivors. Besides, for ethical and practical reasons, the authors could only select participants through snowballing thanks to a gatekeeper, namely a general practitioner who offered to select persons of his trust deemed fit for this study. Other respondents could have had other interpretations of their experiences. But it has to be emphasized that the strength of this study is in the depth of the narratives provided by respondents.

Notwithstanding the above, the authors ensured that bias was avoided in the research process. The standard procedures of semi-structured interviewing were carried out, and responses were analysed systematically in relation to the conceptual framework of the study. Given the nature of this study, it was concluded that face-to-face interviews were more appropriate than other methods, so as to ensure maximum trust from respondents.

The interviews were conducted in the first months of 2013. All respondents were asked the same questions in the same order. Some respondents required prompting and further explanation of certain questions.

The first questions were descriptive, thus focusing on the respondents' background. These were followed by questions on the respondents' reactions to their cancer diagnosis and on their social relationships with relatives and medics. Respondents were then asked about their lives before and after cancer and about their experiences as cancer patients. Subsequently, respondents were asked about coping with cancer and about their outlooks about their respective futures.

The process commenced with two-pilot studies from which no problems emerged. One particular respondent required assistance from his spouse who articulated his thoughts. All interviews were recorded and the case-summary method was used for transcription.

In most cases, respondents were interviewed alone, but there were some cases when a respondent's spouse would be present for the respective interview. Interviewees were asked questions directly linked to the scope of this article together with other questions related to coping strategies and self-identity.[31] All interviewees except one were open and looked comfortable in sharing their experiences during Cancer. The exception regarded a respondent whose responses were made by his spouse as she stated that he was very introvert and preferred keeping things for himself.

Through their sociological imagination, the authors of this study believed that respondents' views would be very much related to the severity of their cancer, to their general outlook on life and to their social situations such as family background. These opinions helped inform the research questions of the study, but only after a thorough literature review was carried out, thus informing the research process systematically. On the other hand, certain findings went beyond what authors were expecting. A striking example was one which emphasized the support given by cancer patients to their significant others, as explained later on in this article.

It is important to emphasize that even though responses provided a high degree of validity, due to the production of information which reflected the real life experiences of cancer patients, the responses can in no way be deemed as being representative of cancer patients in Malta and beyond.

Findings

Mixed Social Interactions

The cancer experience had mixed impacts in terms of participants' interactions in social life. Some carried on with their regular social activities, whilst other withdrew from social interaction apart from that concerning their family life. Yet most participants did not feel stigmatised by others. But this only happened because they did not disclose their illness to non-family members, as they feared the social repercussions of being exposed. Hence, the spectre of stigma haunted some participants of this study.

One universal commonality among participants was their expressed need to communicate about their illness with their respective families. They felt the need to open up about their respective cancer experiences.

Karen Mifsud, for example, wanted to be left alone at times, but also wanted to open up about her experience with someone. Family members were very important in this regard. The same line of thought was expressed by other participants who did not feel comfortable talking to non-family

members about their illness. One participant, Nadine Borg, had told her neighbours and friends when she had previously experienced appendix, after she spent time in hospital. But she did not do the same when she experienced cancer.

Participants such as Noreen Galea and expressed their need for quiet, away from the everyday social interaction.

> *"I avoided people to avoid talking about my illness and also I looked for quiet places away from people".*

Yet, other participants felt the need to disclose their cancer experience to strangers, friends and neighbours.

Manuel Falzon, for example, said that he did not mind speaking about his cancer experience with such persons. As he put it, "there is nothing to be ashamed of". Claudia Bugeja's perception was along the same lines, stating that she talked about her experience with different people she encountered.

Natasha Vassallo stated that she felt more comfortable discussing her experience of Cancer with other patients who were going through the same experience.

> *"At first, I kept everything for myself but then I found someone going through the same experience and gave me the strength not to give up".*

Some others felt that if they spoke up about their experiences, this could be beneficial to other cancer patients. An interesting example in this regard was of Joe Borg. An introvert personality, he relies very much on his wife for social interaction. And his wife actually related to his experiences to encourage other cancer patients to face their situation with a positive attitude.

Strengthened Family Bonds

All of the participants participating in this study argued that Cancer brought their family members closer to each other, strengthening their bonds.

Most participants found support from their families. Families provided support for the former Cancer patients.

> *"After being diagnosed with Cancer, bonds between family members became stronger and cohesive... I wanted to spend as much time as possible with my family. During my illness, relatives used to call or visit every day to check up on me"* (Mandy Cauchi).

Some other participants, especially thouse whose cancer was diagnosed in its early stages, did note any major difference in their family relationships. A case in point was Craig Thomas who was diagnosed with skin cancer.

The fact that most family members provided support to the participants is hardly surprising, also especially due to the strong family bonds that exist in Maltese society. However, participants showed that their situation was not simply dictated by a one-way process of relatives providing assistance to patients. Indeed, most participants stated that their illness initially had a negative impact on their relatives, who experienced sadness, fear, anxiety and anger. Many felt lost and preoccupied about their loved ones' chances of survival. Hence, coping strategies for relatives of patients were also required.

One of the participants, Manuel Falzon explained that his wife shared his cancer experience with their relatives on her family side. This was mainly the case as she herself needed to cope with this new situation, and thus felt the need of support from relatives.

Participants gave importance to their family bonds in relation to the provision of courage and determination to fight the illness. For example, Karen Mifsud said that she fought against cancer "*because I have my daughter to live for*". In such cases, family relationships provided a sense of obligation.

Another participant, Noreen Galea was concerned about her children's thoughts, questions and anxieties related to her illness. Indeed, there were cases where family members felt more scared and lost than the patients themselves. Manuel Falzon's wife, for example, stated that

> *"When my husband was diagnosed with Cancer, I felt more scared than him, especially during the first treatment of chemotherapy."*

Mandy Cauchi asserted that

"Even though my husband always acted courageously, during Cancer, he needed my help to survive".

Rose Tanti expressed how her illness affected her son's behaviour. He "*became distant and withdrew from his friends and social activities*".

Therefore, apart from being reliant on the support of family members in relation to their illness, participants in this study asserted that support was two-way, as they themselves helped their family members to cope with the situation. In a clear case of reciprocity, respondents relied on family support but, in turn, were also a source of support for their loved ones.

Besides, the cancer experience also helped relatives become more aware of the illness, and in some cases encouraged them to conduct checkups more frequently.

As regards family relationships, therefore, the cancer experience had some unintended positive outcomes. Family members tended to get close together, and support was two-way, where cancer patients themselves often provided support and encouragement to their loved ones in their coping strategies.

Discussion and Conclusion

The findings of this research show that social networks of cancer sufferers may be of great value as they provide support and reciprocity. This is two-way, as apart from the support given by relatives to sufferers, this study also revealed that sufferers can offer moral support and encouragement to their loved ones as they try to cope with the new situation.

In this regard, Putnam emphasizes the value of social networks characterized by people's relationships. He refers to "connections among individuals- social networks and the norms of reciprocity and trustworthiness that arise from them".[32]

Judging by the findings above, chronic illness can also be theorised in terms of positive and unintended outcomes. In this regard, Merton's theory of latent and manifest functions is of great relevance.[33] Manifest functions have intended consequences, yet society is also characterised by latent consequences, which were not expected or intended.

In the case of cancer sufferers, example of latent consequences were the development of new friendships with other patients, the increased closeness with family members, and the support given by sufferers to their own relatives.

This research has shown that social interaction of cancer survivors in Malta is characterized by mixed experiences, but at the same time, all cancer patients emphasized the importance of family support. A major finding of this research is that cancer patients do not simply receive support from family members, but also provide it themselves to their relatives. This is not an intended effect of cancer survivorship, but nevertheless it helps strengthen social bonds within families of cancer patients.

Given the importance of family bonds among cancer patients, it is recommendable that Health authorities invest more in counseling and other support services to families experiencing such situations, and in providing functional equivalents for cancer patients who do not have close family bonds. Therefore, Malta's welfare system should ensure that social networks of trust are universally accessible to all cancer patients, irrespective of their social background.

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Original Article

Safety monitoring of the newer Disease Modifying Therapies in Multiple Sclerosis patients in Mater Dei Hospital

Daniela Zammit, Josanne Aquilina

Abstract

Patients with highly active Multiple Sclerosis can be started on the newer pharmaceutical agents, Dimethyl Fumarate or Fingolimod. Safety monitoring recommended includes regular blood analysis and also ophthalmic tests and MRI scans in the case of Fingolimod.

The aim of this audit is to verify whether timely investigations are being taken, checked and results documented in a database and whether the appropriate action is being taken should safety become a concern.

Method: An Excel document shared by all four Neurology consultants documents the patients' personal details, any baseline investigations or other recommended tests taken and the blood results taken at regular intervals. This data was analysed for accuracy by keeping it up to date. The products' SPC recommendations were used as guidelines and the time-frame modified locally.

Results: After analyzing all the blood tests taken while on Dimethyl fumarate, 39% of patients took their regular blood tests on time; 31% were not taken on time and 30% had no blood tests taken at all. On the other hand, only 59% of patients on Fingolimod took their blood tests on time. 82% of the blood results were documented in their Excel document. A repeat MRI scan 6 months after starting Fingolimod showed that only 53% took it on time.

Conclusion: Using an Excel document was a trial to try and ensure compliance with these recommendations. However, this audit clearly documents that it is not enough to follow patients on a regular basis, highlighting the need for a specialist nurse to monitor such patients.

Keywords

Multiple Sclerosis; medical audit; Dimethyl fumarate; Fingolimod; Malta

Abbreviations

Multiple Sclerosis (MS); Central Nervous System (CNS); Summary of Product Characteristics (SPC); Progressive Multifocal Leukoencephalopathy (PML); Complete Blood Count (CBC); Urea & Electrolytes (U&E); Liver Function Tests (LFT); Magnetic Resonance Imaging (MRI); Disease-Modifying Agents (DMA's); Upper Normal Limit (UNL).

Introduction

Multiple Sclerosis (MS) is a chronic, autoimmune, inflammatory, demyelinating neurological condition of the central nervous system (CNS) whereby the T-cell mediated immune system destroys the myelin and axons in varying degrees. MS is a progressive disorder that has an unpredictable and varied course. Initially, the symptoms are reversible as demyelination heals incompletely; however, prolonged demyelination

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causes axonal loss and clinically progressive symptoms. The trigger is unknown, although it is thought to have a combination of genetic predisposition and environmental factors, such as a viral infection early on in life.[1]

The mean age of onset is usually between 20 to 40 years [2] and women are twice more likely to be affected than men.[3] It has a higher prevalence in Caucasians and in temperate countries such as Northern European countries, possibly linked to low levels of circulating Vitamin D.[1]

There are four major categories of MS based on the course of the disease:[4]

1. *Relapsing-remitting MS* (85% of patients): The most common form, it is characterised by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission.
2. *Secondary progressive MS*: may develop in patients with RRMS as the disease progresses. Periods of remission lessen and symptoms may not disappear completely as disability accumulates.
3. *Primary progressive MS* (10% of patients): There is a steady decline as symptoms continue to worsen from the start of the disease with no relapses/remissions, although there may be occasional plateaus. This is the most challenging type to manage as it is resistant to most drugs used in MS.
4. *Progressive-relapsing MS* (5% of patients): This rare form of MS is progressive from the start with intermittent flare-ups along the course and no periods of remission.

MS has a wide range of symptoms and signs on presentation but it usually presents monosymptomatically.[1] Patients can present with visual symptoms such as diplopia, unilateral optic neuritis; sensory disturbances including dysthaesia (burning and "pins and needles") or paraesthesia (numbness or tingling); motor symptoms such as leg weakness; or also brainstem or cerebellar symptoms including ataxia, vertigo, tremor etc.

Early on, relapses may be followed by remission and full recovery. Since it is a progressive disorder, with time remissions becoming shorter and less frequent and may not return back to normal in between flare-ups as disability accumulates.

At Mater Dei Hospital, the new Disease-Modifying Agents (DMA's) used in highly active relapsing-remitting multiple sclerosis include Dimethyl fumarate and Fingolimod. According to the Summary of Product Characteristics (SPC) of Dimethyl fumarate, one of the precautions mentioned include close monitoring of the patients' blood tests at regular intervals to look out for lymphopenia, changes to the hepatic and renal function, and MRI imaging if at increased risk of Progressive Multifocal Leukoencephalopathy (PML). The SPC of Fingolimod also recommends regular blood tests to look out for lymphopenia and hepatic impairment. In addition, all patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of Fingolimod in view of the risk of bradyarrythmia, MRI imaging to assess for the risk of PML, and an Ophthalmology review after 3 months of starting treatment to look out for macular oedema. In view of the serious consequences that may arise should any shortcomings occur, the Neurology consultants within Mater Dei Hospital started an Excel document to try and ensure compliance with these safety measurements.

Methods

Approval was sought from the Data Protection Office and University Research Ethics Committee, with endorsements from all four Neurology Consultants. An Excel document shared between the four consultants keeps track of all patients on Dimethyl fumarate and Fingolimod. It documents patients' personal details, starting date of treatments, any baseline investigations or other recommended tests taken, and blood results taken at regular intervals. The products' SPC recommendations are used as guidelines to identify what tests are needed to be taken regularly.

The time-interval was set as bi- or tri-monthly, as agreed between the consultants. The results were either documented as "on time" (i.e. taken within the 30-day period of that month), "not on time" (i.e. outside of the 30-day window), or "not taken" (no blood results taken 1 month before or after the anticipated month were found). All blood tests were taken at Mater Dei Hospital and the results were found on the computer programme iSoft Clinical Manager; thus excluding any tests performed in the private sector. Patients that stopped treatment or were lost to follow-up did not have any further blood tests taken regularly. According to Fingolimod's SPC recommendations,

patients should have a repeat MRI after 6 months of starting medication to ensure there is no relapse/disease progression.

The Excel document was accessed during the first week of January 2016 and any data inputted up to this date was analysed for accuracy, kept up-to-date with the latest blood results, and any documented actions taken, without consulting each patient's personal Medical file.

Results

Dimethyl fumarate

The bar graph in *Figure 1* was created to show how many of the 38 registered patients on Dimethyl Fumarate had their blood tests actually taken on time, how many were not taken on time, how many were not taken at all and how many are still pending at timely intervals (x-axis). No clear pattern is observable, however one can note that over time there were less tests taken (on time and not on time) while there are increasing pending tests in view of new patients being started on Dimethyl fumarate.

Since one cannot assume or predict how the pending tests will behave, as either taken on time or not on time, our existing data needs to be interpreted without taking them into consideration. Therefore, after deducting the pending tests, the pie-chart in *Figure 2* shows that up to 39% of the tests taken so far were done in a timely fashion; whilst, 31% of such tests were not taken on time according to the predetermined timeframe. Moreover, up to 30% of the regular assessments were not taken at all since no results were shown on iSoft. Therefore, altogether up to 70% of tests were taken whilst one-third have lost their opportunity to be adequately monitored for any abnormalities (*Figure 2).*

Fingolimod

From the blood tests actually taken, 68 out of 115 total tests were taken on time, making up just 59% of the total tests. On the other hand, a little less than half of the tests were not taken on time, as 47 tests out of 115 tests, i.e. 41% of them, were taken at an earlier or later date than the predetermined timeframe *(Table 1) (Figure 3).*

If one were to analyse whether blood tests results were chased, acknowledged and documented in their Excel database, one will find that the majority (i.e. 82%) were clearly documented whilst only 18% were found to be not documented in their database. The results were found in iSoft Clinical Manager, indicating that the patient had taken the test but it was unclear whether the result was chased by the firm *(Table 2) (Figure 4).*

Out of 23 patients registered, only 19 had their 6-monthly MRI taken, of which 10 were taken on time, 3 were taken at an *earlier* date whilst 6 had the MRI taken at a *later* date. The MRI date was late by 1 month at the lowest and 4 months by the highest. These would tally up to 53% of the MRI's taken on time, 16% taken at an earlier date and 32% taken late *(Table 3) (Figure 5).*

Figure 1: Blood tests taken at set intervals for Dimethyl Fumarate

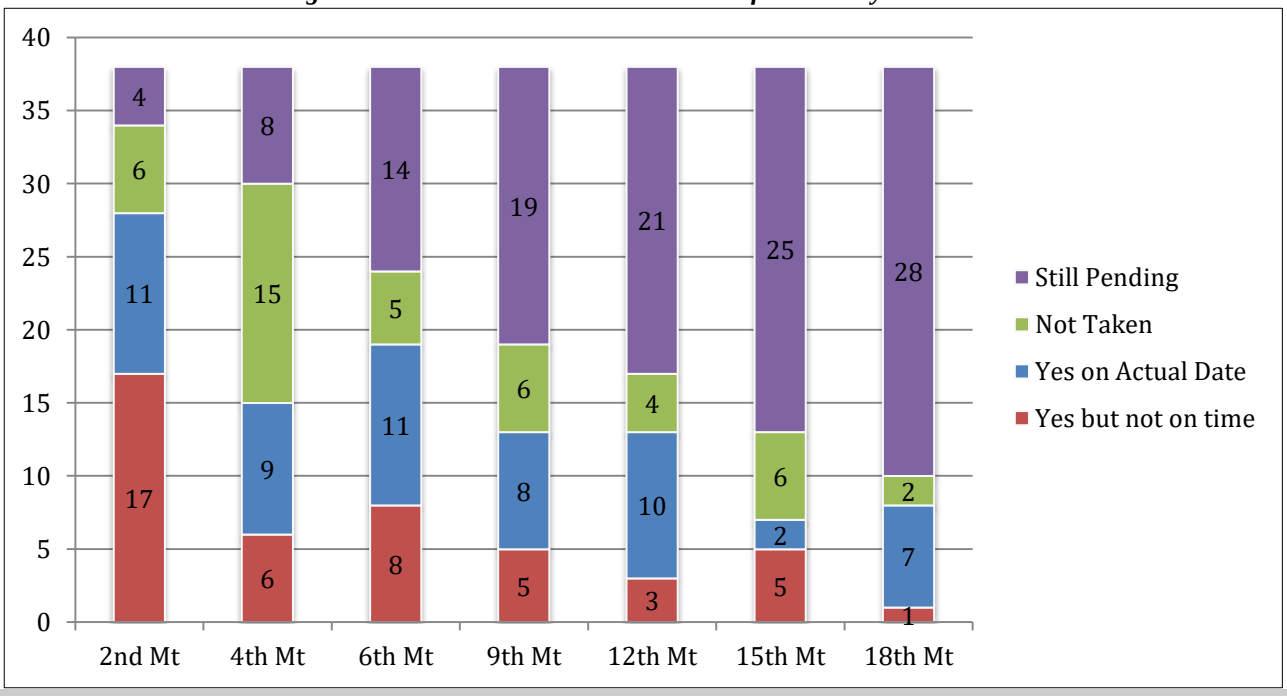


Figure 2: *Percentage for total blood tests booked for Dimethyl Fumarate*

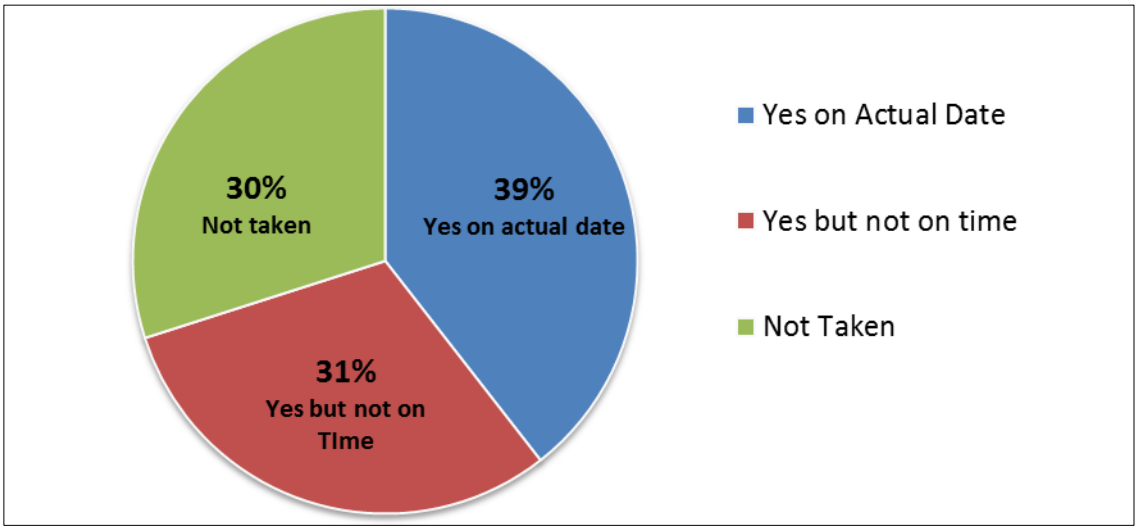


Table 1*: Timely blood tests taken on Fingolimod treatment*

Timely Blood tests		
Blood tests taken on Time	**68**	**59%**
Blood tests NOT taken on time	**47**	**41%**
Total tests performed	**115**	

Figure 3*: Timely blood tests taken for Fingolimod*

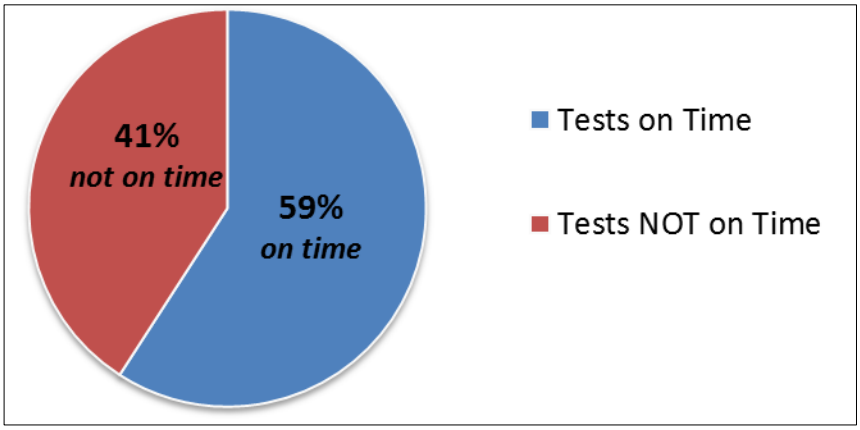


Table 2*: Blood test documentation in Excel database on Fingolimod*

Blood test result documentation in Excel database		
Result documented	**94**	**82%**
Result not documented	**21**	**18%**
Total results available	**115**	

***Figure 4**: Result Documentation in Database for Fingolimod*

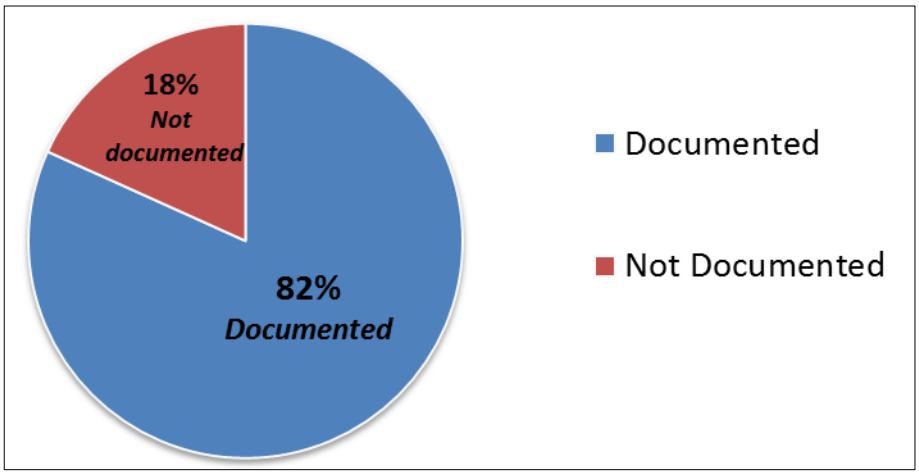
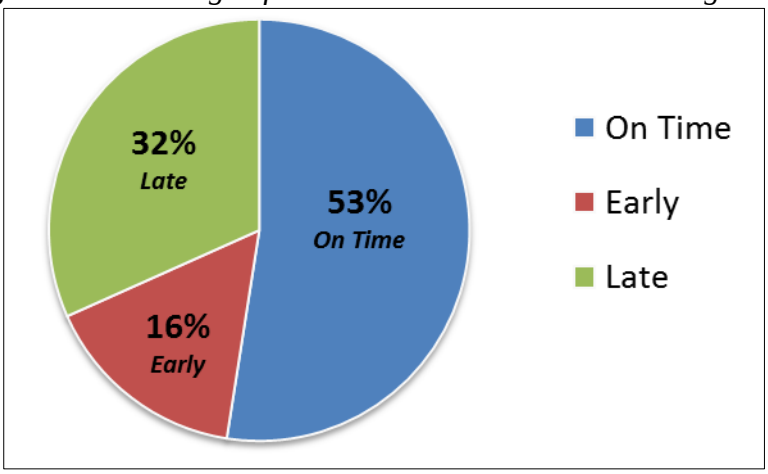


***Table 3**: 6 months MRI surveillance while on Fingolimod*

6 Months MRI surveillance		
Total patients performed	**19**	
MRI taken on time	**10**	**53%**
MRI taken at an earlier date	**3**	**16%**
MRI taken at a later date	**6**	**32%**

***Figure 5**: Percentage of 6-Months MRI scan while on Fingolimod*



Discussion

Dimethyl fumarate - (Tecfidera®)

After collecting and interpreting all the data, a number of observations were noted. In a few cases, not all three blood tests (CBC, U&E, Cr and LFT's) were taken as baseline before starting treatment, taken regularly every month or screened for any abnormalities from their baseline.

While in their database it was stated that baseline bloods were available on a particular date, on three occasions these could not be traced on the iSoft programme, raising the question whether they were actually taken and the source of their claim. In other instances, the starting date of treatment was not stated in the Excel database. There were cases where the predicted timeframe for due tests did not correspond with the starting date of treatment as documented in their database. This made it debatable whether treatment was actually started on the date as stated, or whether the tests were routinely taken 1 month later.

While searching for their regular blood tests on iSoft, it was noted that some of the values were not documented on their Excel database, raising

concerns whether they were chased and acknowledged. Moreover, some lymphocyte results were not documented in the right tab on their Excel database – For example, the 2nd and 4th month results were swapped.

On three occasions, the lymphocyte count was noted to drop below 0.5 $x10^9$/L. Despite this, no action was documented in their Excel sheet as to whether this treatment was temporarily suspended to allow the lymphocyte count to recover, as advised by the product's SPC recommendations.

Some patients had pending blood tests showing on iSoft Manager for the upcoming months, while for the majority they had no upcoming blood tests ordered. This raised concerns on how compliance was monitored and whether checks were made to ensure patients had an appointment set for blood-letting.

Fingolimod - (Gilenya®)

Similarly to Dimethyl fumarate, not all three blood tests (CBC, U&E, Cr and LFT's) were taken as baseline before starting treatment, taken regularly every month or screened for any abnormalities from their baseline. 10 patients out of the total of 23 did not have documentation of their 3-month ophthalmological examination, whether it was performed or the exam's conclusion in the Excel document.

Some MRI tests did not have their results documented in their Excel database, making it uncertain whether they were chased and acknowledged in a timely fashion. 16% of the 6-monthly MRI were taken earlier, possibly performing it during a suspected relapse when the patient exhibited signs and/or symptoms.

Not all patients had blood tests booked on iSoft programme for the upcoming months. This made it difficult to ensure compliance from the patient to take their blood tests on time. On 7 occasions in total, the blood test results documented on their Excel database did not match the true results as taken from the iSoft computer programme. In one case, two sets of results were swapped as the 6th and 9th month result respectively. While searching for patients' regular blood tests on iSoft, it was noted that some of the values were not documented on their Excel database, thus raising concerns whether they were chased and acknowledged.

In two cases, the lymphocyte count had dropped less than 0.2 $x10^9$/L (0.16 and 0.17) with no documented action keyed into their database. On the other hand, two particular patients were documented as "monitoring lymphocyte count and to decide on further management". One of these had discontinued Fingolimod indefinitely in view of recurrent lymphopenia.

After 12 months, according to the consultants' database it states any further blood tests to be taken as "regular follow-up". However, there was no clear pattern as to how often this should have been taken. In fact, some tests were sparsely taken and in other occasions were taken too close to each other to observe for any abnormalities. Only one consultant kept a regular time-frame after the 12th month, which made it easier to keep track of the patient's blood tests and MRIs due.

Conclusion

The use of Dimethyl fumarate and Fingolimod require a number of investigations to be taken before starting treatment to ensure that the right candidate is eligible for these DMA's. In addition, close follow-up of these patients with regular blood tests, MRI scans and an ophthalmological review are necessary to ensure no complications arise. The SPC recommendations are clearly documented and any shortcomings can have serious consequences.
In view of this, the consultants within the Neurology Department felt the need to utilise an Excel document as a trial to try and ensure compliance with these recommendations. However, this audit clearly documents that it is not an easy task as it is quite time-consuming and laborious. As a result, the Excel document was not used appropriately, and clearly it is not enough to follow patients on a regular basis.

Therefore, the suggestions below may help to alleviate the problem and ensure better compliance in the future;

1) A qualified specialist nurse would be highly beneficial to educate, support and advise patients to take regular blood tests and stress the importance of compliance. He/she would work with the professional backup offered by Neurologists should a problem arise.
2) Ensure each patient has a set of baseline blood tests, including **all** three tests (CBC, U&E, LFT's), taken before initiating therapy.
3) **All** three blood tests should be regularly booked and screened for any abnormalities

during their appointment, namely the lymphocyte count and the liver hepatic enzymes.

4) Patient should be provided with set appointments according to the timeframe set in the Excel database and if they do not show up by mid-month, they can be reached via phone/email/SMS and reminded of their appointment.
5) Once the test has been taken, the result should be chased and acknowledged by the nurse and inputted in the Excel database in the correct order.
6) Should there be any concerns, the nurse can discuss the issues with the Neurologist for any action required. These should then be clearly documented in the Excel database for future reference.
7) The specialist nurse would also act as the point of contact should the patient report any symptoms or signs of an infection to check their latest lymphocyte count, concerns about the treatment's side-effects, queries about appointments and any other information required about their condition.
8) Patients on Fingolimod, should have regular Liver Function Tests taken and assessed for any abnormalities. Results should be documented in case there are elevated liver enzymes which if >5 times UNL, would necessitate suspending treatment temporarily as advised by the SPC recommendations.
9) In view of a high rate of patients suffering from Diabetes Mellitus locally, such patients taking Fingolimod would benefit from regular ophthalmological examinations and not just as baseline and at 3-months of therapy. Macular oedema may develop with or without visual disturbances.

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Review Article

Fetal MRI: an essential step in interpreting complex ultrasound findings

Ian Baldacchino, Isabelle Saliba, André Stefan Gatt

Abstract

Background: Fetal magnetic resonance imaging (MRI) allows for the interpretation of complex fetal anomalies detected on ultrasound (US). Locally it has been available since 2013 but has remained underused.

Method: In this paper we report the US and MRI findings of all cases of fetal MRI that were taken to date locally and how MRI can contribute to the clarification of malformations, management, counseling, evaluation of prognosis and ruling out of other possible malformations.

Results: The cases reported were: two cases of hydroureter; gastroschisis; ventriculomegaly; intracranial haemorrhage; splenic cyst; Arnold Chiari II malformation. In all seven cases MRI was able to add to or change the diagnosis.

Conclusion: Fetal MRI acts as an adjunct to US in interpreting abnormal fetal development. It is a safe non-invasive method of imaging that allows the clinician to take more informed decisions and better parental counselling.

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MeSH terms

Child, Counseling, Magnetic Resonance Imaging, Pregnancy, Prognosis.

Introduction

Locally fetal magnetic resonance imaging (MRI) has been available since 2013. This allows for the possibility of interpreting fetal anomalies detected on ultrasound (US). In this paper we report all fetal MRIs taken to date locally.

Routine US is first line in detecting fetal anomalies being fast, safe, inexpensive and avoiding any form of ionizing radiation. It cannot however give more subtle information when attempting to focus on a specific organ or region of fetal anatomy and is limited by the experience of the user, maternal obesity and oligohydramnios.[24,27] MRI also has its downfalls being hindered by fetal movements, requiring a long scan time of 50-60 minutes and fasting period of two hours.

Fetal US

Fetal US employs high frequency pulsed sound. The propagating waves encounter different tissues and are reflected back to be picked up by a transducer. The waves are then depicted on a screen which allows the interpreter to see the strength of the signal and its position. Safety during the first trimester is ensured by employing lower power output devices and ensuring a short 'dwell time' over a particular target.[29] US in pregnancy is indicated for two main reasons: routine US screening; diagnostic examination following identification of abnormal growth, complications during pregnancy and risk factors for fetal malformation. Early first trimester US (<24 weeks) aims at planning the pregnancy by giving a better evaluation of gestational age and identifying multiple pregnancies and has demonstrated a reduction in the rates of medical inductions. Routine US in later pregnancy is not recommended.[8]

Fetal MRI indications

The decision to undertake fetal MRI is dependent on the following care decisions:

1. The decision about treatment, mode of delivery, eventual prognosis and parental counselling, can be clarified further when US is not enough to confirm diagnosis
2. When the abnormality detected on US appears complex and the physician wishes to make more better informed decisions about patient care
3. There is a considerable risk for abnormality of the fetus even if US scans are normal.[13]

More specific indications are listed in Table 1 but each case merits its own individual attention.

Fetal development in MRI

Fluid filled organs including the oesophagus, bowels and bladder appear hyperintense on T2-weighted MRI and hypointense on T1-weighted MRI containing mineral and protein rich meconium produced after 13 weeks gestation (WG). Therefore bowel situated outside the body will transmit these appearances respectively.[12] The liver similarly is rich in iron as well as other minerals such as zinc and will show alike T1- and T2- appearances. It has a characteristic moderately dark structure on T2-weighted MRI.[22,26] A homogenous signal can be detected on T2 weighted images when assessing for the spleen after 20WG appearing hypointense on T1- and hyperintense on T2- weighted images.[22]

Renal abnormalities may account up to 14-40% of prenatal abnormalities and is often accompanied by deficincies in liquor volume. MRI can be useful in clarifying the severity of disease and confirm the presence or absence of structures.[1,5-6,10] Therefore the diagnosis and management of cases can be changed as MRI was more adequate in assessing the size and degree of hydroureter indentified by higher signals on balanced fast field echo (bFFE) and single shot sequences.[10,21]

Fetal brain anomalies identified on ultrasound often still remain indeterminate in nature. Also ultrasound reverberations onto the more anterior hemisphere from overlying bony structures interferes with optimal visualisation allowing only the more distal hemisphere to be visualized. Later on the ossifying calvaria make fetal MRI a more tempting alternative.[15,27] Ventriculomegaly is the commonest non-specific finding on fetal central nervous system (CNS) ultrasound which can indicate other conditions that can be diagnosed by MRI.[3] Prenatal sonography can then go on to interpret other findings in 80% of cases associated with other syndromes such as Dandy-Walker complex, lissencephaly etc however cortical abnormalities such as agenesis of the corpus callosum, cortical malformations, intraventricular haemorrhage etc still remain sonographically occult, being identified only on MRI.[16-17,27]

MRI preparation

Fetal MRI predominantly applies T2-weighted imaging. Single shot fast spin-echo (SSFE) is the most useful modality providing T2-weighted images that capture cross-sectional segments which may be disrupted by fetal movements.[24] When required, Fast Multiplanar Spoiled Gradient-Recalled imaging provides T1-weighted images for identification of fat, haemorrhage and calcification.[9,18,23,28]

Fetal MRI images were obtained on a 1.5 Tesla scanner (GE Healthcare, Milwaukee, Twin Speed version HDX). The patient is asked to fast for two hours to minimise fetal movement artefacts and then positioned supine wearing an 8 channel torso coil. A 3 planar localizer is used. Calibration: Coronal SSFSE ARC; Sagittal SSFSE ARC; Axial SSFSE ARC.

Fetal MRI ethics

The pediatric society of radiology recommends that fetal MRI be performed after 18 weeks gestation (WG). Effects on the developing fetus are still unknown. The use of contrast is also not recommended for its safety during pregnancy has not yet been adequately studied. So far however there have been no reported adverse effects on fetal and maternal outcomes during pregnancy in this aspect or on human tissue.[13,25] Other recommendations specify waiting till at least 22WG as knowledge on the subject is still lacking, also small size and excessive motion of young fetuses make imaging difficult to interpret.[16]

***Table 1**: Indications for fetal MRI [4,20]*

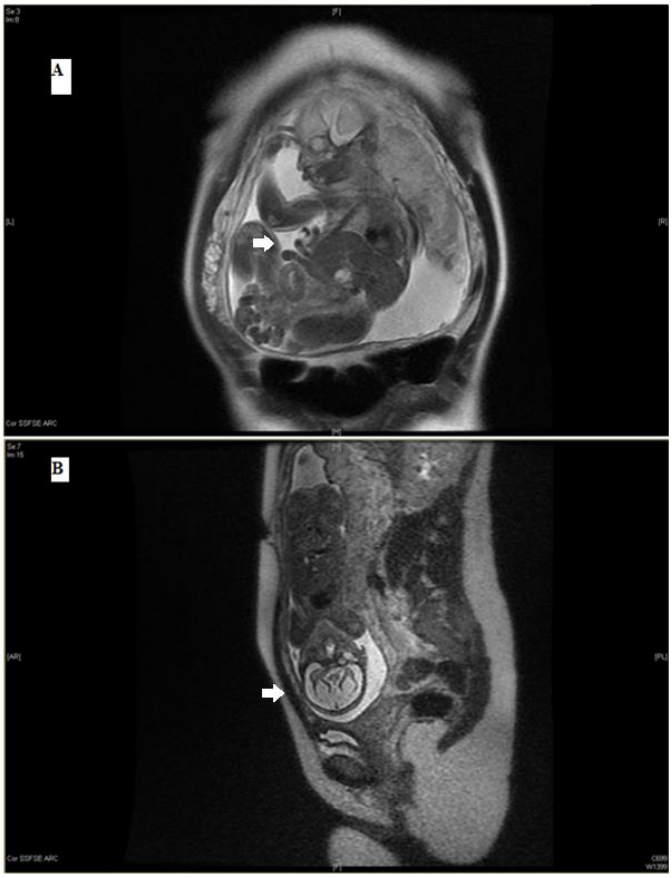
System	Main indication category.	Subcategory
Central nervous system.	Brain development.	cell density, myelination.
	Vascular anomalies.	haemorrhage, ischaemic lesions, monochorionic twin pregnancy complications
	Screening fetuses with a family risk of brain anomalies.	Tuberosclerosis, corpus callosum developmental anomalies.
Fetal oropharynx and face.	Airway patency.	Reviewing compromise by masses, mandibular or facial malformations.
	Confirm or diagnose isolated cleft of the posterior palate.	
	Other anomalies.	Atypical facial clefts, retrognathia, micrognathia, craiosynostosis, cephaloceles, vascular anomalies, tumours, microphthalia, other ocular and orbital anomalies.
Neck.	Masses relative to fetal airway.	Assist in managing delivery, assess fetal goiter and thyroid neck masses.
Thoracic anomalies.	Provide more information for counselling and management on malformations.	Bronchopulmonary sequestration, congential pulmonary adenomatoid malformation, oesophageial atresia.
	Congenital diaphragmatic hernia.	Evaluate lung volume and presence of liver and intra-abdominal organs in the thorax. Assess lung growth.
Fetal heart.		Fetal echocardiography remains the method of choice for screening and evaluation of anomalies.
Intra-abdominal anomalies.	Masses.	Reserved for when US cannot provide information for adequate counselling or management. Review of cystic or solid masses including tumours.
	Urogenital tract.	Readily visualized on US however low liquor volume,e fetal position may distort adequate assessment. MRI can help in this situation.
Extremities and Bone.		US is imaging of choice however MRI sequences have also been developed.
Spine.	Congenital anomalies.	US is modality of choice to screen for neural tube defects. Suspected anomalies can be confirmed on MRI including neural tube defects, sacrococcygeal teratomas, vertebral anomalies.
Complications of monochorionic twins.		Assess vascular anatomy; review co-twin for morbidity; review anatomy in cojoined twins.

Case reports

Case 1: 28WG with confirmed gastroschisis on ultrasound showing a 7mm defect on the right side of the umbilicus. On fetal MRI the defect was evidently much larger. It was able to also detect partial herniation of the right lobe of the liver and right kidney as well as herniation of multiple small bowel loops and the dome of the urinary bladder. Diaphragmatic hernias and pulmonary dysplasia were excluded. Perinatal care was planned for. (Figure 1A)

Case 2: A 23WG investigated for the demise of one twin which was accompanied by ventriculomegaly in the second twin on US. MRI confirmed ventriculomegaly as well as enlargement of the extra-axial spaces. There was also however marked thinning (perceived absence) of large areas of the supratentorial cortex which represented extensive cortical loss through infarction. (Figure 1B)

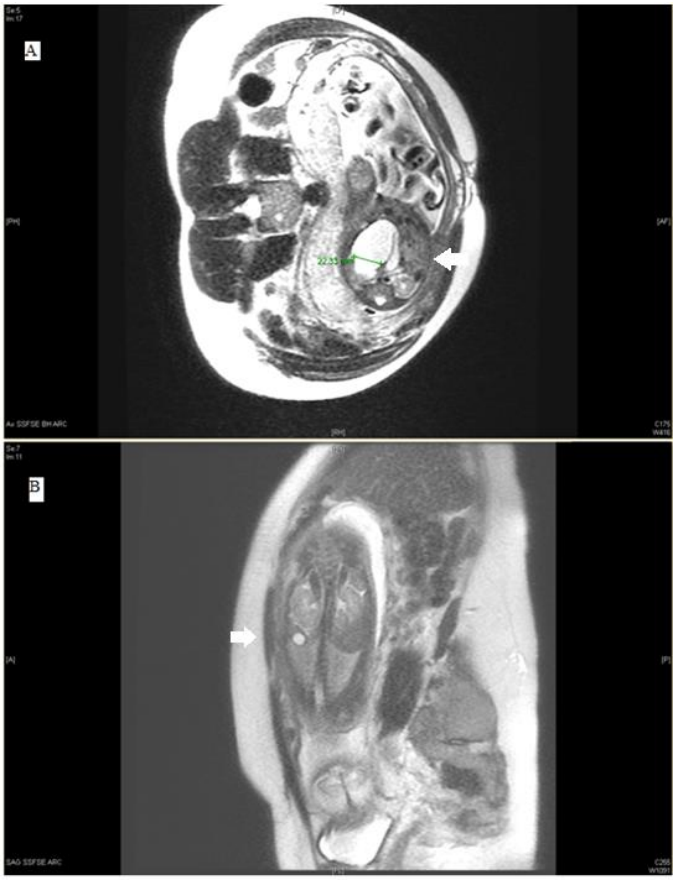
Figure 1(A): *Gastroschisis depicting herniation of multiple bowel loops and dome of urinary bladder* **(B):** *Ventriculomegaly and thinning of the cerebral cortex consistent with infarction*



Case 3: 24WG identified with an enlarged right sided kidney and findings indicative of obstruction. The MRI was able to confirm the diagnosis the degree of hydronephrosis (Figure 2A). The size and orientation of the kidneys was confirmed as well as the architecture of the right kidney.

Case 4: A cystic lesion was identified behind the stomach on US however the exact detail as to which organ was involved was inconclusive. Fetal MRI corroborated this with a 10mm cyst lying in the upper pole of the spleen consistent with a simple splenic cyst. It was also able to rule out other organs being involved and confirmed the benign nature. (Figure 2B)

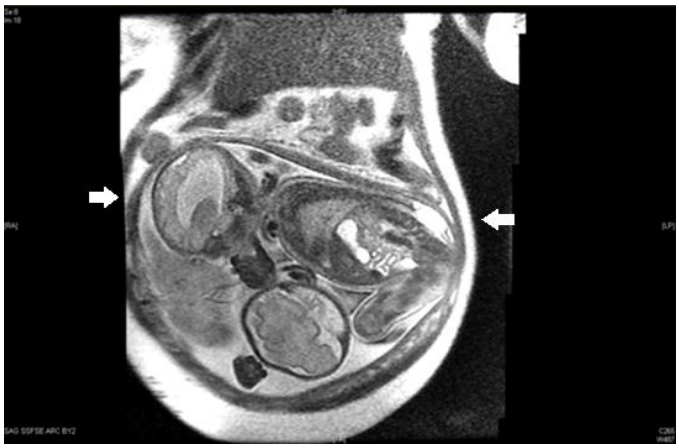
Figure 2: (A) *Marked hydronephrosis of the right kidney* **(B)** *Splenic cyst*



Case 5: A lower lumbar lesion was identified on a twin consistent with spina bifida. MRI demonstrated a lumbosacral myelomeningocele and meningeal sac as well. It also added that there was associated hydrocephalus and cerebellar tonsillar herniation diagnosing a Chiari II malformation (Figure 3A). No abnormalities were identified in the other twin. The anomaly was confirmed at birth and

the twin transferred to a more supportive unit.

Figure 3: *Sagittal view depicted hydrocephalus and cerebellar tonsillar herniation – Chiari II malformation and myelomrningocele*



Case 6: 23WG presented with sudden increase in biparietal diameter (BPD) which was reported as fetal hydrocephalus on ultrasound with skull bossing. An anechoic cystic structure in the cerebellum possibly obstructing the fourth ventricle was also identified. MRI was able to confirm a right sided haemorrhage associated with smaller blood products in the contralateral ventricles suggesting a communicating hydrocephalus secondary to blood products (Figure 4A and 4B). The diagnosis was changed as well as the management of the case.

Case 7: 26WG referred in view of dilatation of both kidneys on ultrasound. The right renal collecting system was however reported as normal on MRI however the left side was only mildly dilated. The prognosis of the case therefore improved and ruled out obstructive pathology involving the bladder and ureters. The case required simple follow up.

Discussion

In the seven cases presented all had an initial anomaly that was identified by US. In all cases MRI was able to add to or change the diagnosis.

In the first case US was only able to report a small defect of 7mm. MRI however confirmed a more appropriate 7cm opening along with several viscera herniating outside the abdominal cavity. This anomaly arises from a discrepancy in the space allocated for the viscera and the viscera in the abdominal cavity, and can also be associated with other respiratory complications.

Figure 4: (A) *Axial view showing left sided brain dilatation pushing against the skull vault* **(B)** *Sagittal view showing extent of haemorrhage*

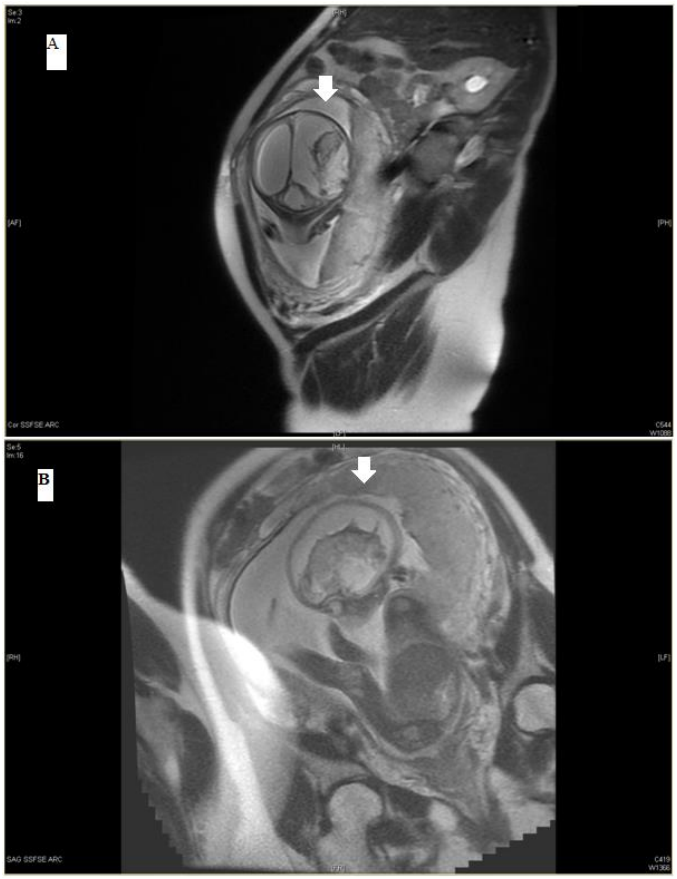
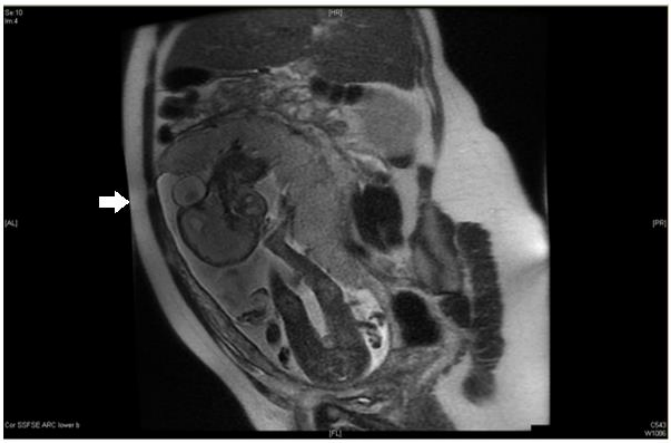


Figure 5: *Meningoencephalocele containing part of the cerebellum*



Gastroschisis is a defect which affects all the layers of the abdominal wall (in contrast to omphalocele where the abdominal organs fail to return into the abdominal cavity at 11WG). At birth the main concerns are the stabilization of the patient and the exclusion of other congenital anomalies.[15] In the UK the preferred means of correction is by silo followed by surgical corrective means. The size

of the defect, presence of intestinal atresia, intestinal necrosis or perforation which are usually evident at birth and are associated with gastroschisis influence which method, be it surgical or silo repair, be undertaken.[7] The latter were evaluated for by MRI.

Cases 2 and 7 displayed abnormal renal findings. The 'Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilatation' reports that the anterior – posterior renal pelvis diameters (APRPD) are reported as abnormal if ≥4mm in the second trimester and ≥7mm at 32WG. If the APRPD is ≥7mm at 32WG there was a general consensus recommending postnatal radiological evaluation. If the APRPD ≥10mm after 48 hours postnatally it was considered as abnormal. Milder degrees of dilatation may still require follow up even later on in life wtih a diameter of 3mm being normal for a one year old and 6mm for a six year old (values based on MRI measurement). It was also observed that progressive urinary tract dilatation during pregnancy (rather than lack of regression) was more associated with uropathies. The management would then include follow up ultrasonography and consideration of surgical or medical intervention (ex antibiotic prophylaxis).[19]
Central nervous system and spinal anomalies such as Arnold Chiari malformations and cerebral haemorrhage are confirmed via MRI. Echogenic structures such as blood clots (referring to case 6) could be interpreted for cystic structures and are clarified on MRI. MRI is clearer in cases of intracranial haemorrhage and more accurate than US with worse grading after MRI was performed.[11] In this way expecting parents are counseled about the possible outcomes, management available and prognosis. Specialised obstetric care and birth management can be planned ahead. Nearly all myelomeningoceles have the Arnold-Chiari II malformation which is associated with other antenatal anomalies and long term disability. Options include prenatal or postnatal correction of the meningocele. The former has to be balanced against the risk of preterm delivery and maternal morbidity.[2] Case 6 was then confirmed to be a case of intracranial haemorrhage, shifting the diagnosis from a structural cause. Drug exposure, viral infection and thrombotic causes were excluded eventually leading to the detection of severe fetal thrombocytopenia when fetal blood sampling was carried out.

Conclusion

Fetal MRI acts as an adjunct to US in interpreting abnormal fetal development. It is a safe non-invasive method of imaging that allows the clinician to take more informed decisions and better parental counselling.

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Ms.Suzanne Attard and MRI team at Mater Dei Hospital.

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Review Article

Endoscopic bronchial ultrasound in mediastinal staging of lung cancer

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Abstract

Lung cancer is a global healthcare concern with a low 5-year survival rate and a high proportion of advanced-stage cases at diagnosis. In the absence of distant metastasis, the most important prognostic marker is mediastinal lymph node involvement. Timely diagnosis and staging improves prognosis, making rapid, safe, and accurate investigation essential.

Endoscopic bronchial ultrasound (EBUS) is a minimally invasive technique which allows for ultrasound-guided transbronchial needle aspiration (TBNA) during bronchoscopy, with cytological sampling of several intrathoracic groups of lymph nodes. EBUS reduces need for open surgical biopsy, with good sensitivity and specificity and excellent safety profile.

This article reviews current evidence regarding use of EBUS in lung cancer staging, including its role in other intrathoracic malignancies.

MeSH terms

ebus, lung cancer, nsclc, staging, lymphadenopathy

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Introduction

Despite advances made in oncology and aggressive anti-smoking public health campaigns, lung cancer remains a significant burden in terms of patient morbidity and mortality. 2012 saw an estimated 1.6 million deaths worldwide from the disease, and incidence is increasing, with a projected 3 million fatalities predicted in 2035, mainly in the developing world.[1] Especially of concern is the fact that average 5-year survival for all kinds of lung cancer is as low as 10-20%, with little variation in prognosis between developed and developing regions.[2] The local data is similarly bleak: incidence of lung cancer in Malta is on the rise, especially in women – and it is associated with an even more worrying increase in mortality.[3]

Lung cancer can be divided into small cell and non-small cell lung cancer, the former accounting for around 20% of cases and carrying a worse prognosis due to its usual late stage and inoperability on diagnosis.[4] Comparatively, 48% of non-small cell lung cancer patients in the UK have stage IV disease on diagnosis,[5] but keeping in mind that early stage I disease has a 72.5% 1-year survival rate, the importance of rapid diagnosis and staging is highlighted.

The most widespread staging classification in use for lung cancer is the TNM staging system, shown in table 1.[6] Nodal status is the most important prognostic marker in the absence of metastatic disease, as only patients with N0, N1 and very selected cases of N2 disease are amenable to surgery, which is the definitive curative treatment.[7] If surgery is not an option, patients should be referred for chemotherapy, radiotherapy, or a combination, with the intent of cure or palliation.[8] Thus, accurate nodal staging is crucial to guide the best possible selection of treatment.

Conventional staging of lung cancer had so far included the use of CT, PET-CT, radiology-guided transthoracic biopsy and flexible bronchoscopy to determine extent of disease. Some centres offer mediastinoscopy under general anaesthesia. This is

available in the Maltese healthcare system, but is falling out of favour due to its invasive nature. However, there is significant delay, unnecessary investigation, and cost burden associated with multiple tests,[9] and this creates a niche for an investigation that can provide extensive information at one go. Since its introduction in 1992, endoscopic bronchial ultrasound (EBUS) has become increasingly useful in this regard, providing excellent information with regard to both diagnosis and staging of lung cancer in one procedure. This year marks the introduction of EBUS in the Maltese healthcare system, with expected benefits in investigation of malignant and benign conditions alike.

Table 1: *TNM staging (Adapted from TNM7 staging system[6])*

Primary tumour (T)	
TX	Primary tumour cannot be assessed, or the tumour is proven by the presence of malignant cells in sputum or bronchial washing but is not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤ 3cm in greatest dimension, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion more proximal than the lobar bronchus (not in the main bronchus)
T1a	Tumour ≤ 2 cm in greatest dimension
T1b	Tumour > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumour > 3 cm but ≤ 7 cm or tumour with any of the following: - Invades visceral pleura - Involves the main bronchus ≥ 2 cm distal to the carina - Associated with atelectasis/obstructive pneumonitis extending to hilar region but not involving the entire lung
T2a	Tumour > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumour > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumour > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, parietal pleura Or tumour in the main bronchus < 2 cm distal to the carina but without involvement of the carina Or associated atelectasis/obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe.
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, or carina; or separate tumour nodule(s) in a different ipsilateral lobe
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in contralateral lobe; tumour with pleural nodules or malignant pleural/pericardial effusion
M1b	Distant metastasis

Endoscopic bronchial ultrasound

EBUS allows for real-time visualisation of the bronchi, mediastinum, and lung parenchyma using an ultrasound probe attachment during flexible fibreoptic bronchoscopy. The concept of concurrent endoscopy and ultrasonography is not limited to bronchoscopy; the use of endoscopic ultrasound (EUS) for the gastrointestinal tract is established and has also been introduced in Malta.[10] Together, these two counterparts provide access to good-quality imaging and biopsy of mediastinal lymph nodes previously only achievable with invasive surgical staging.

There are a large variety of EBUS probes available on the market, but these can be broadly classified into radial probes (RP-EBUS) and convex probes (CP-EBUS). Radial probe EBUS has the advantage of higher-resolution (20-30MHz) circumferential imaging with better distal access. On the other hand one cannot perform real time ultrasound during biopsy using this technique.[11] Conversely, CP-EBUS (figure 2) is a larger, lower-frequency 7.5MHz probe with better interventional utility, as transbronchial needle aspirations (TBNA) can be carried out with concurrent ultrasound guidance, improving safety profile and diagnostic yield compared to blind TBNA.[12]

Figure 2: *Convex-probe EBUS*

Convex-probe EBUS-TBNA technique

EBUS is carried out as a day procedure under conscious sedation or general anaesthesia. Contraindications to the procedure are few and similar to those of conventional bronchoscopy, summarised in table 2. Because of a theoretical risk of bleeding during TBNA, the current practice is to withhold antiplatelet agents and anticoagulants prior to the procedure.[13] By convention, aspirin and warfarin are stopped for three days pre-procedure, with bridging heparin for warfarinised patients for whom omission of warfarin is contraindicated, and clopidogrel is stopped one week prior.

Table 2*: Contraindications to EBUS-TBNA*

Contraindications to EBUS-TBNA
Current or recent myocardial ischaemia
Severe hypoxaemia
Haemodynamic instability
Severe pulmonary hypertension
Poorly-controlled heart failure
COPD/asthma exacerbation
Life-threatening dysrhythmias
Patient on anticoagulation/antiplatelets (not stopped)
Clotting abnormalities
Intolerance to sedation/anaesthesia

During the procedure, potentially malignant lymph nodes can be identified by the following characteristics: round shape, heterogeneous echogenicity, distinct margin, presence of coagulation necrosis sign (a hypoechoic area within an enlarged node showing absence of Doppler signal).[14] Absence of all four features carries a 96% chance that the visualised node is benign. Once a potentially abnormal node is identified, this may be biopsied with a retractable 21 or 22 gauge needle introduced through the bronchoscope. The needle is then used to puncture the bronchial wall and pierce the suspicious node under ultrasound guidance. Suction is applied to obtain a cytology specimen, with at least three punctures per lymph node recommended to maximise yield,[15] following which the needle is retracted. The procedure can be repeated for other abnormal nodes as needed.[11]

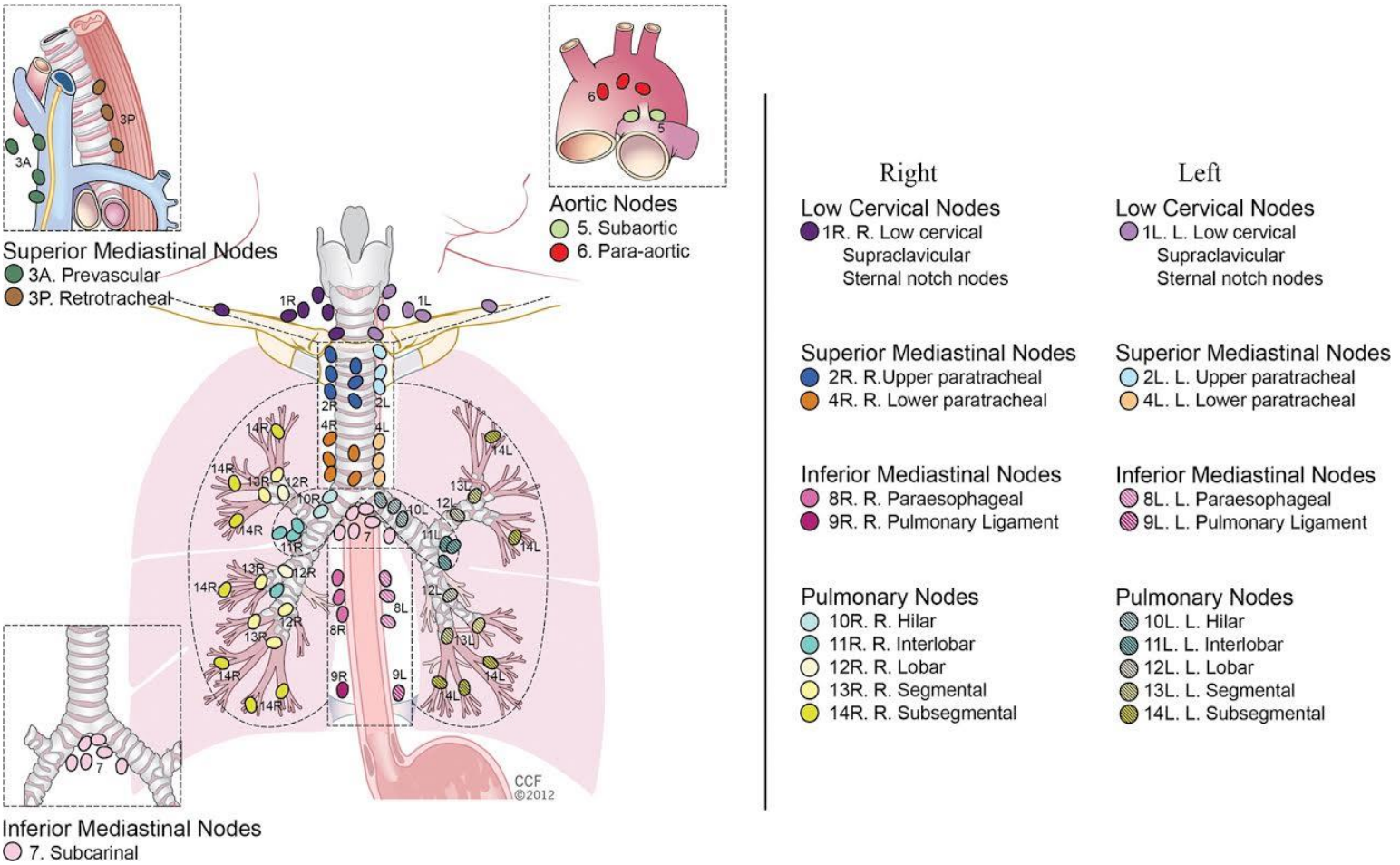
The specimen obtained from EBUS-TBNA is a cytology specimen, which is handled in liquid fixative like conventional TBNA or transthoracic needle biopsy samples. In order to maximise tissue yield, manufacturers are developing new needles for

use in difficult-to-diagnose pathology such as lymphomas or rare cancers.[16] Despite the current unavailability of histology specimens from EBUS-TBNA, much information can be obtained from good-quality samples. A retrospective, multicentre study of 774 patients showed that 90% of EBUS-TBNA samples were suitable for endothelial growth factor receptor (EGFR) testing and 77% were sufficient for subtyping with staining and immunohistochemistry.[17]

Some specialised centres also offer rapid on-site evaluation (ROSE) for EBUS-TBNA specimens, with review of samples during the procedure for e. While there are no current clinical trials available, several smaller-scale studies have reported that ROSE increases diagnostic yield in a cost-effective manner, with less strain on the pathology service due to insufficient samples.[18-20]

Examination of lymphadenopathy during EBUS requires a good working knowledge of the anatomy of cervical and intrathoracic lymph nodes. The current convention is the International Association for Study of Lung Cancer (IASLC) lymph node map, published in 2014,[21] seen in figure 1. The system describes 14 lymph node groups, or stations in the neck and chest, categorised into 7 zones, which may be involved in local and regional spread of lung cancer.

***Figure 1**: Reproduced from IASLC mediastinal lymph node map[21]*



It is important to note that, while EBUS provides excellent access to certain lymph node stations, it is not technically possible to gain access to all of them, and other techniques such as EUS may be required to access lower thoracic stations. Table 3 summarises lymph node stations accessible to different investigation modalities.[22]

Keeping in mind that different procedures access different nodes, there is an increasing question as to whether EBUS and EUS should be performed together in order to maximise accuracy and completeness of staging. A 2015 meta-analysis of 10 studies with 1080 participants showed that combination EUS and EBUS showed a significantly higher sensitivity for staging of lung cancer of 91% compared to 80% in EBUS alone, without significant increase in complication rate.[23,24]

However, this raises some concern as to

whether such extensive investigation is necessary in all cases. A 2010 US study used software models to compare cost-effectiveness between combined EUS-EBUS and EUS alone and reported that combining the two procedures is more cost-effective in cases where there are enlarged mediastinal lymph nodes on CT, while absence of lymphadenopathy favours the use of EUS alone.[25]

***Table 3**: Access to lymph node stations by procedure*[22]

Station	EBUS	EUS	Mediastinoscopy	Video-assisted thoracoscopic surgery (VATS)[a]
1 – Low cervical, supraclavicular, sternal notch	*		*	
2 – Upper paratracheal	*	*	*	
3 – Prevascular, retrotracheal	*	*		*
4 – Lower paratracheal	*	*	*	*
5 – Subaortic		*	* [b]	
6 – Para-aortic		* [c]	* [b]	
7 – Subcarinal	* [d]	* [e]	*	*
8 – Para-oesophageal		*		*
9 – Pulmonary ligament		*		*
10 – Hilar	*			*
11 – Interlobar	*			
12 – Lobar	*			
13 – Segmental				
14 – Subsegmental				

[a] Unilateral access only
[b] Extended mediastinscopy only
[c] Requires trans-aortic biopsy
[d] Anterior subcarinal nodes
[e] Posterior subcarinal nodes

Which investigations to use for staging?

The 2014 Scottish Intercollegiate Guidelines Network (SIGN) guidelines for management of lung cancer states that a CT scan of the thorax and abdomen should be requested in patients with suspected lung cancer regardless of chest X-ray result. Chest CT is regarded as being positive for mediastinal lymphadenopathy with nodal size >10mm short axis diameter. However, the guideline acknowledges the high false positive and negative rates for diagnosing abnormal nodes on CT (45 and 13% respectively)[26] and recommends use of PET-CT scan in patients being staged before radical treatment, which has the benefit of a low false negative rate of 5%.[26] Patients with >10mm nodes on CT and/or positive uptake of FDG on PET should be considered for mediastinal nodal sampling for definitive staging, as combined PET and CT have sensitivity of 61% and specificity of 96% for positive mediastinal nodes.[27] The guideline recommends the use of EBUS-FNA with or without EUS-FNA for endoscopic assessment of suspected mediastinal involvement prior to mediastinoscopy.[26]

Prior to EBUS gaining popularity, surgical staging with mediastinoscopy was regarded as the gold standard investigation of possible metastatic mediastinal lymphadenopathy, but this is changing.[28,29] This day procedure involves the insertion of a rigid mediastinoscope through the suprasternal notch under general anaesthesia, with direct visualisation of the upper mediastinum and biopsy of abnormal tissue. However, increasing evidence backs the use of endosonography prior to invasive surgical staging, and one of the most important contributions is the 2010 ASTER trial. This shows that combination EUS/EBUS, followed by surgical staging if negative, prevents unnecessary thoracotomy in 1 in 7 patients compared to immediate surgical staging, with

similar sensitivities between the two arms (85% in endosonography versus 79% in mediastinoscopy) and reduced risk of complications in the endosonography (1% versus 6% in mediastinoscopy group).[30]

These findings, coupled with the fact that combined EBUS and EUS are still more cost-effective than mediastinoscopy,[25] would lead one to believe that mediastinoscopy has no further role in staging of lung cancer. However, there is much controversy about the value of a negative EBUS, with varying negative predictive values available in the literature, especially for central tumours.[31-33] The present consensus is that mediastinoscopy should be considered in cases of negative EBUS, but is not an essential step prior to proceeding to thoracotomy; further research is needed to clarify mediastinoscopy's role in modern lung cancer staging.

Perhaps one of the greatest endorsements for EBUS has been the 2015 BOOST trial comparing standard staging investigations, as would be seen in a non-endosonography centre (such CT, PET-CT, conventional bronchoscopy, mediastinoscopy, CT-guided biopsy), with the use of EBUS or EUS immediately following CT. The use of endosonography as an initial investigation was shown to reduce time from first outpatient contact to treatment decision by multidisciplinary team from 29 days to 14, and the EBUS/EUS group was noted to have a lower mean number of investigations per patient, unnecessary thoracotomies, and PET-CT scans. Both groups had the same number of patients being treated with curative intent, but EBUS was shown to be faster, less costly, and – following a post-hoc analysis of patient survival – associated with better post-operative survival compared to patients staged conventionally.[17]

EBUS in small-cell lung cancer

Most studies on EBUS discuss its use in NSCLC due to its better amenability to surgery, but the limited data available on small-cell lung cancer appears promising. In a retrospective analysis of 161 patients, use of EBUS for suspected SCLC showed sensitivity and specificity of 97.4% and 100% respectively, with a negative predictive value of 60%[34], echoing the findings of similar retrospective studies.[35,36] However, the fact that SCLC is often non-resectable at diagnosis often precludes the use of EBUS for workup, making its role not as well-defined as in other tumours.

EBUS in lymphoma

The role of EBUS in lymphoma is highly controversial and guidelines do not currently recommend its use in suspected lymphoma cases.[37] Extensive data is limited but there is concern about high false negative rates, especially in Hodgkin's lymphoma.[38] Sensitivity data is variable but values range from 38%[39] to 86.7%.[40] Much of the problem centres around the fact that accurate diagnosis and subtyping of lymphoma requires histological samples, ideally with excisional biopsy.[41] In fact, the use of ROSE is thought to be beneficial to improve diagnostic yield in lymphoma.[42] There is also a large variability in the design and selection of patients studied, with recurrent cases often being grouped with suspected lymphoma patients, making meta-analysis difficult to design.

EBUS in metastatic extrathoracic disease

EBUS may also be an option for investigation of mediastinal lymphadenopathy in the context of extrathoracic malignancies. A 2014 meta-analysis of 533 patients showed that pooled EBUS-TBNA sensitivity and specificity were 85% and 99% respectively, indicating diagnostic accuracy similar to that in NSCLC.[34] Furthermore, EBUS is capable of delivering samples sufficient for immunohistochemistry and molecular analysis in around 80% of cases.[43]

Conclusion

Although there are still gaps in available evidence, the use of EBUS, with or without EUS, for mediastinal lymph node staging is safe, fast, accurate, and cost-effective. EBUS shortens the time to diagnosis whilst ensuring that patients are staged accurately and referred for the appropriate treatment. Large-scale trials are needed to confirm the usefulness of EBUS in small-cell lung cancer and metastatic extrathoracic malignancy, but the future for this investigative modality appears bright.

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Case Report

Recurrent chest infections in two young non-smoker men

David Sladden, Kevin Schembri, Stephen Montefort, Joseph Galea

Abstract

Pulmonary mucinous cystic carcinomas are rare salivary gland type carcinomas of the lung. They form part of a wide spectrum of mucin secreting glandular mixed type tumours. They comprise 0.1 – 0.2% of all lung tumours. They occur more frequently in young patients and present with cough or recurrent chest infections and therefore may be easily misdiagnosed. Since treatment depends fully on complete surgical resection early diagnosis is essential. Even with treatment the 10-year survival is quoted at 53%. We describe two cases of such rare tumours both of who underwent curative surgical resection. Both patients were younger than 35 years old and presented with recurrent chest infections. The patients were followed for up to eight years and the outcome recorded. A literature search confirms the occurrence in younger patients, who often present with pneumonias and that surgery is the only hope for cure.

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Introduction

Pulmonary mucinous cystic carcinomas are rare but highly malignant tumours. They form part of a wide spectrum of mucin secreting glandular mixed type tumours including mucinous cysts, mucoepidermoid carcinoma, multilocular cystic carcinoma, pseudomyxomatous pulmonary adenocarcinoma and colloid carcinoma.[1] The international association of lung cancer classifies this type of neoplasia as colloid adenocarcinoma.[2] They are salivary gland type carcinomas located within the airways accounting for 0.1 – 0.2% of all lung tumours and for less than 0.1% of all cancer deaths.[3]

Case 1

A 34-year-old male non-smoker with a past history of childhood asthma presented initially in 2007 with pneumonia that was successfully treated. One year later he presented with another chest infection that did not resolve for several weeks, leaving him with a persistent chronic cough (fig 1). CT Thorax showed a narrowed left lower lobe bronchus probably due to carcinoma (fig 2). The diagnosis was confirmed 18 months after the initial presentation with pneumonia. Bronchoscopy showed a white cystic and very vascular mass obstructing the lumen of the anterior segment of the left lower lobe but biopsies were inconclusive. Left lower lobectomy was performed, frozen section of the bronchial margin showed carcinoma and completion left pneumonectomy was performed during the same operative session. On formal histological examination the tumour was shown to be an adenoid cystic carcinoma with colloid laden cystic spaces and compact glandular spaces (fig 3, fig 4). The immunohistochemistry showed positivity for CD 117 and p40, while androgen receptors were focally positive. There was a faint and incomplete immunoreactivity for Her-2 in 20% of neoplastic cells. Malignant cells were present in the pneumonectomy resection margins at the left main bronchus. The tumour was low-grade and the

lymph nodes were tumour free. The patient received adjuvant chemo-radiotherapy. Three years later, metastases were detected in the ipsilateral pleura, contralateral lung and spleen. These were followed by multiple bone metastases and five and a half years following the pneumonectomy the patient passed away due to multiple metastases.

Case 2

A 28 year old male presented with 3 episodes of right lower lobe pneumonias during the previous four years. A CT thorax performed during his first pneumonia showed no tumour or obstruction of the right lower lobe bronchus. The second pneumonia, 4 years later, was investigated solely with a plain PA chest radiograph (fig 5). Upon presenting for the third time 6 months later another CT thorax was taken with contrast. This showed a soft tissue tumour at the origin of the right lower lobe bronchus obstructing the airway (fig 6, fig 7). This was confirmed at bronchoscopy. Biopsies showed squamous metaplasia but no malignancy. A right lower lobectomy was performed one month after diagnosis. Histology showed low-grade mucoepidermoid carcinoma of the lung (fig 8, fig 9). Complete resection was achieved yet post-operative adjuvant treatment was still given on recommendation of the multidisciplinary team. Yearly bronchoscopy and CT thorax have been performed for the past 9 years (since surgery) and no recurrence or metastasis has been detected.

Figure 1: *PA Chest x-ray showing spherical lesion obscured by left cardiac border. This is easily missed if clinical suspicion of tumour is low*

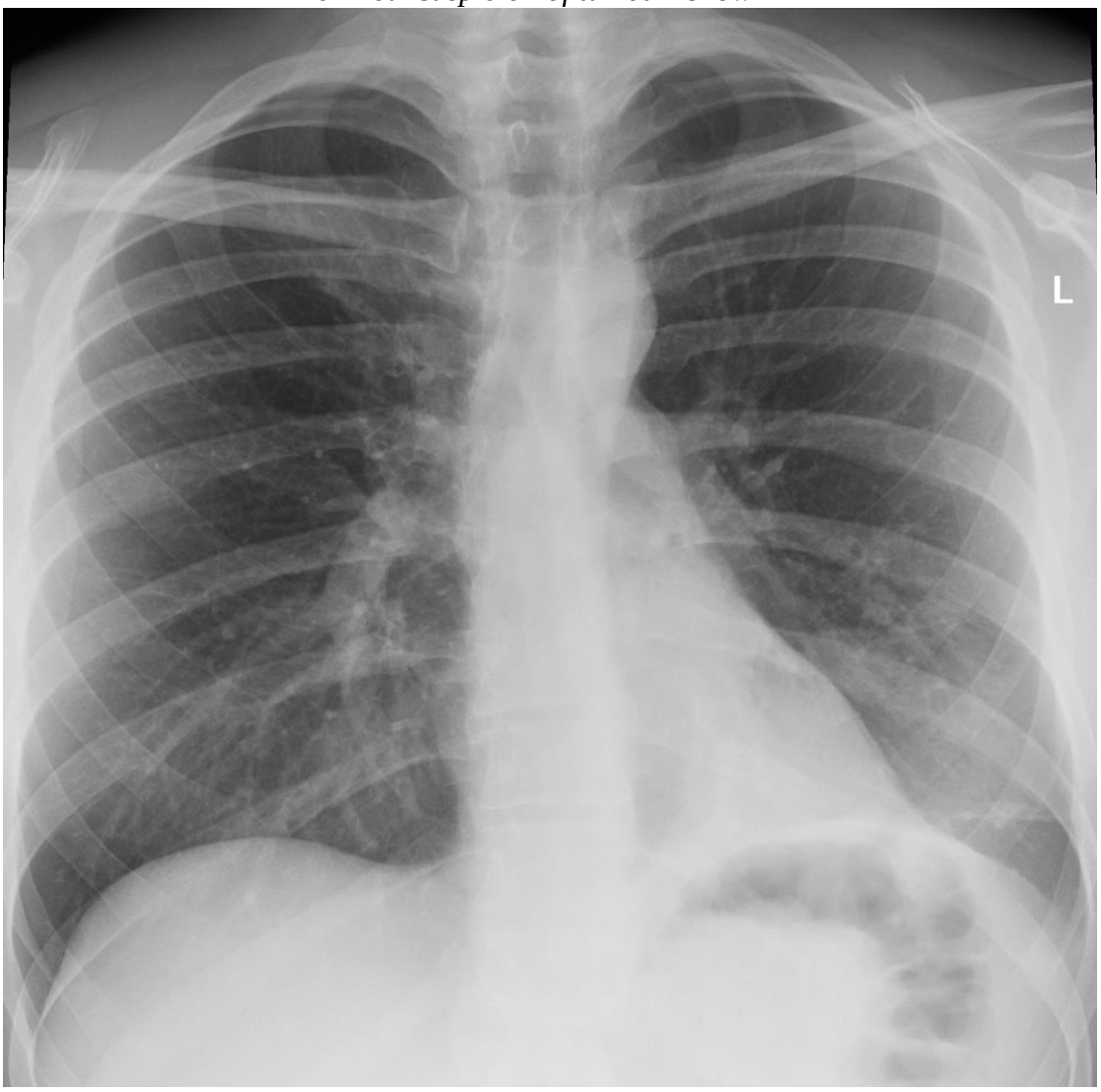


Figure 2: *CT with IV contrast showing the central lesion obscuring the left lower lobe bronchus*

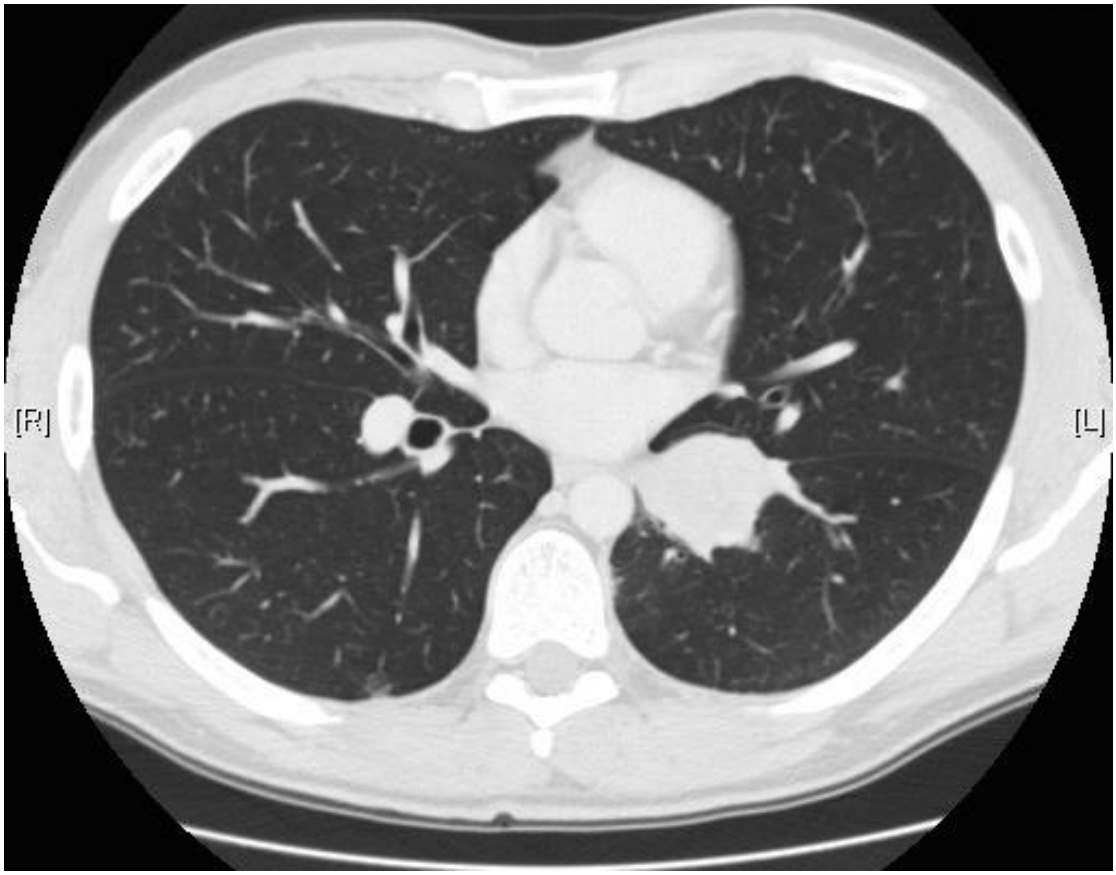


Figure 3: *Adenoid cystic carcinoma of the bronchus (H&E) X 10*

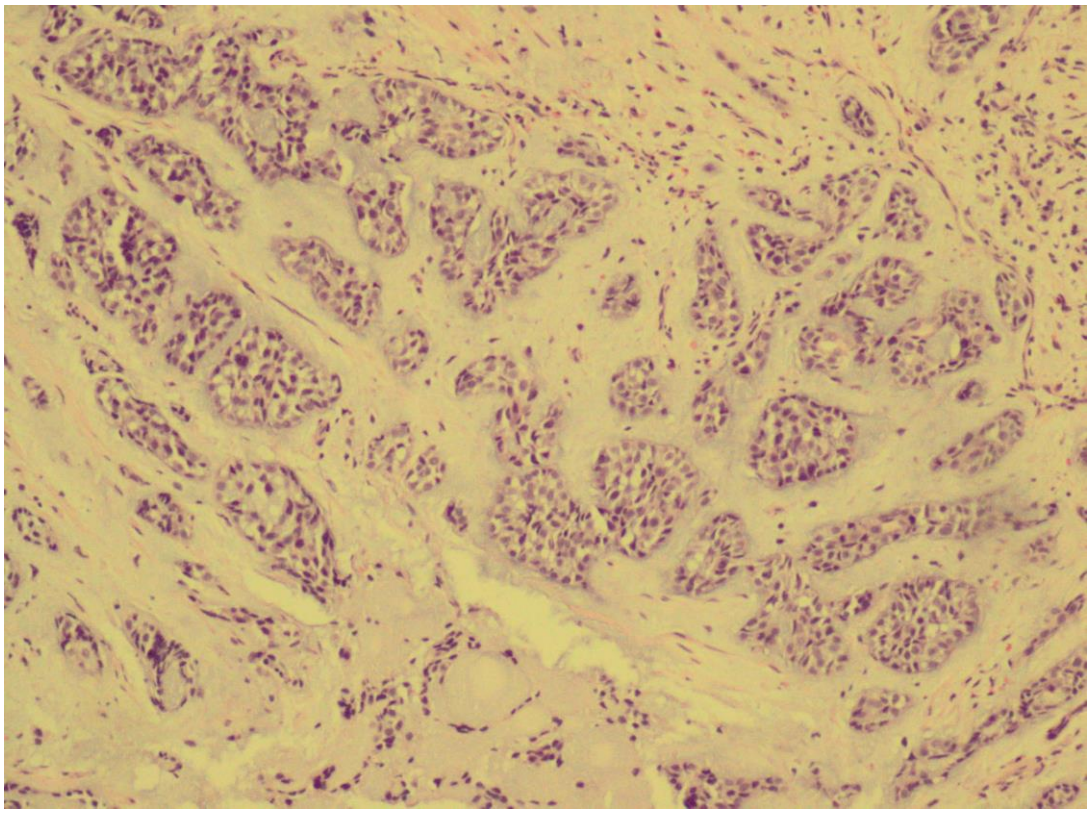


***Figure 4**: Colloid laden adenoid cystic carcinoma of the bronchus (H&E) X 10*

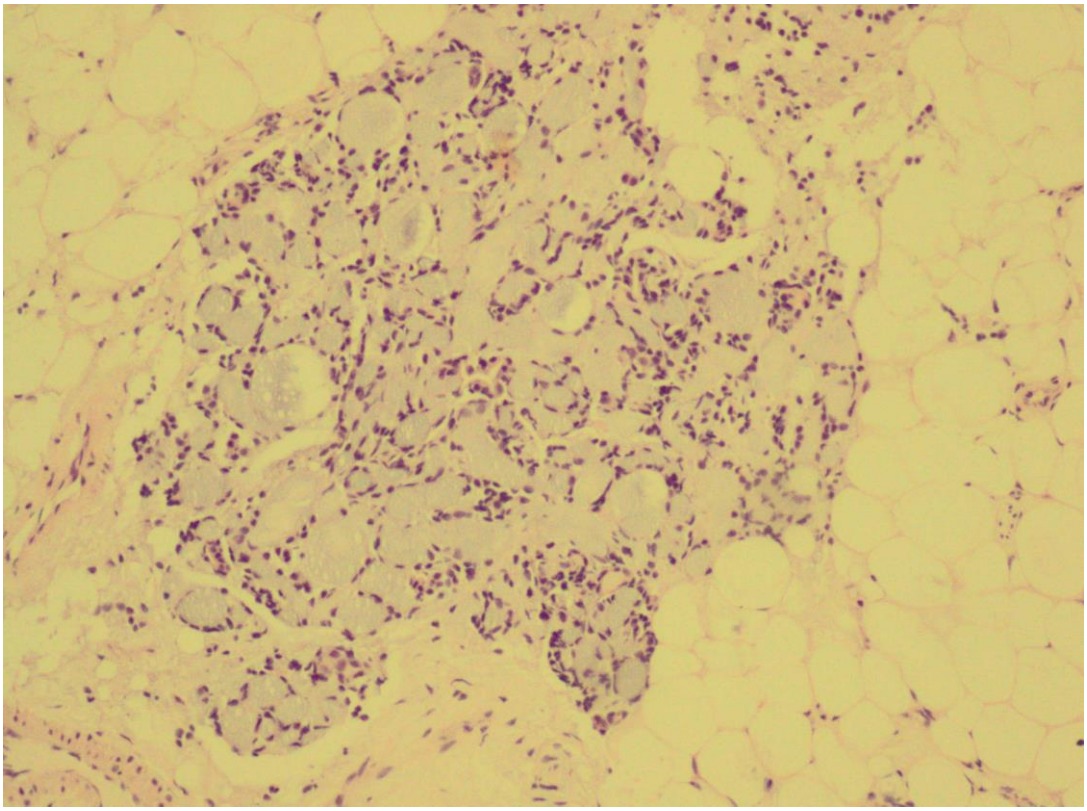


***Figure 5**: PA chest x-ray showing consolidation of pneumonia but no evidence of tumour*

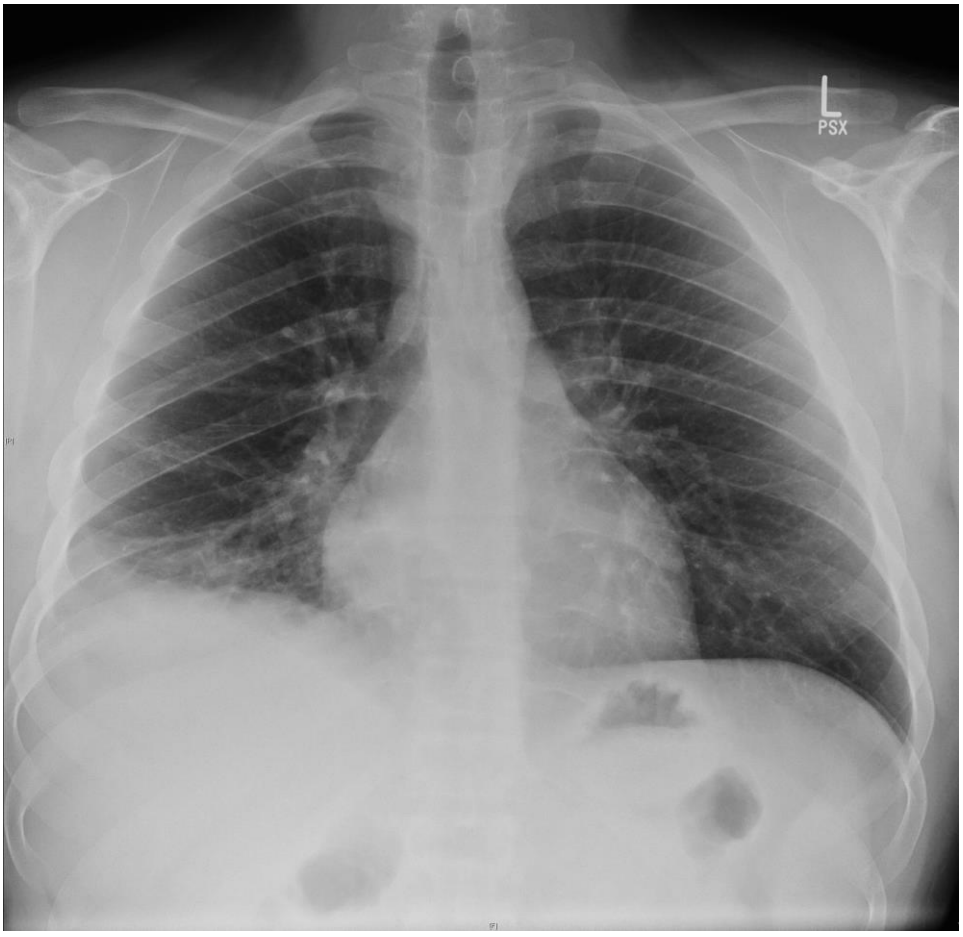


***Figure 6**: CT showing the tumour obstructing the right lower lobe bronchus*

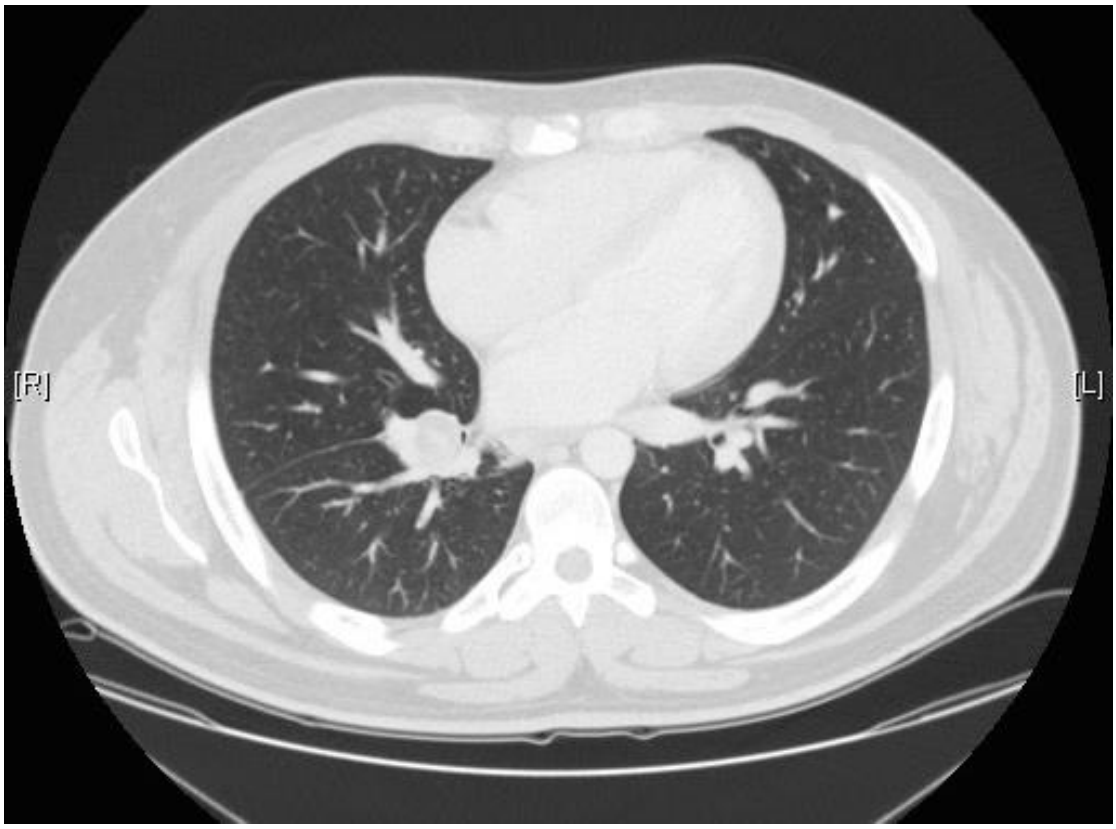


***Figure 7**: CT showing post-obstruction pneumonia of the right lower lobe*

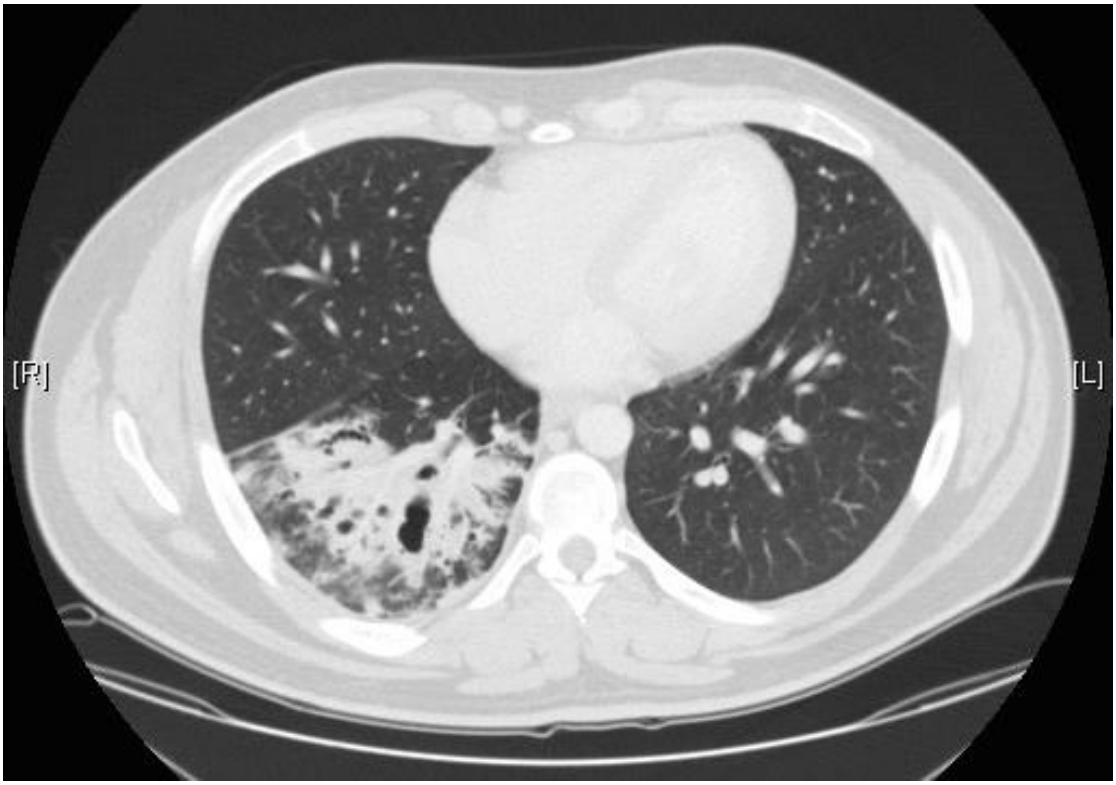


***Figure 8**: Mucoepidermoid tumour of the bronchus (H&E) X10*

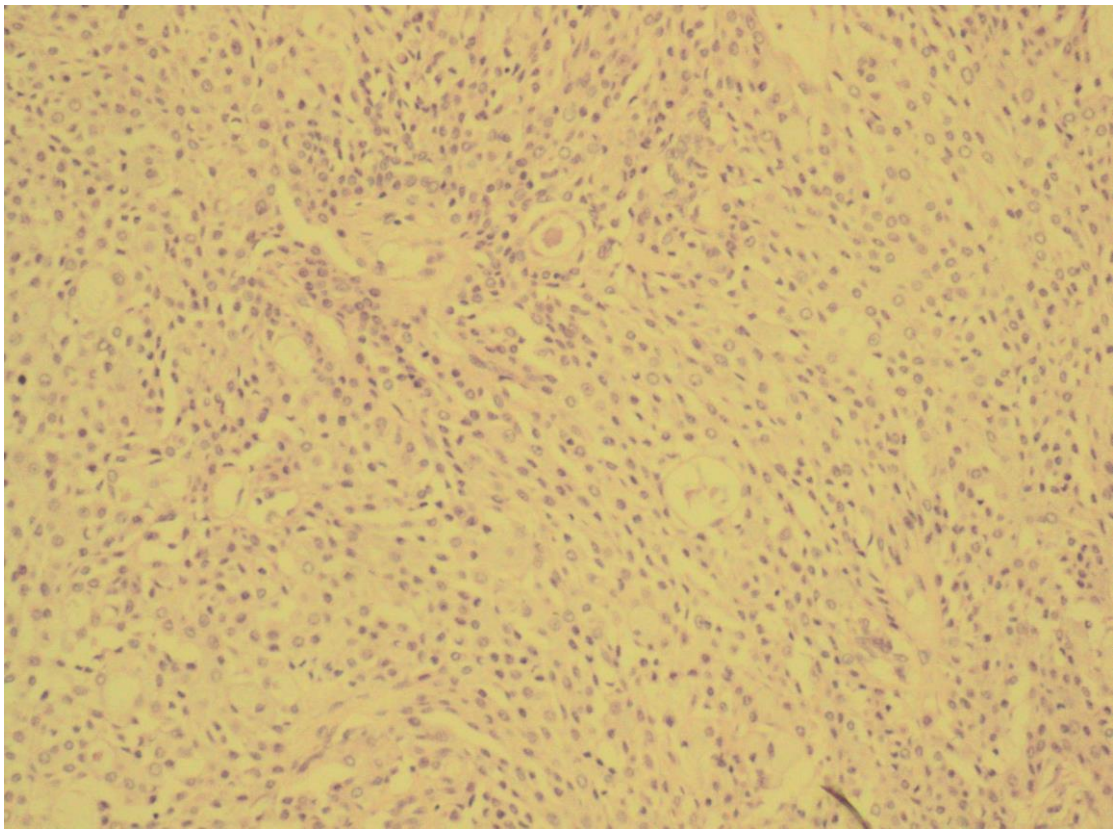
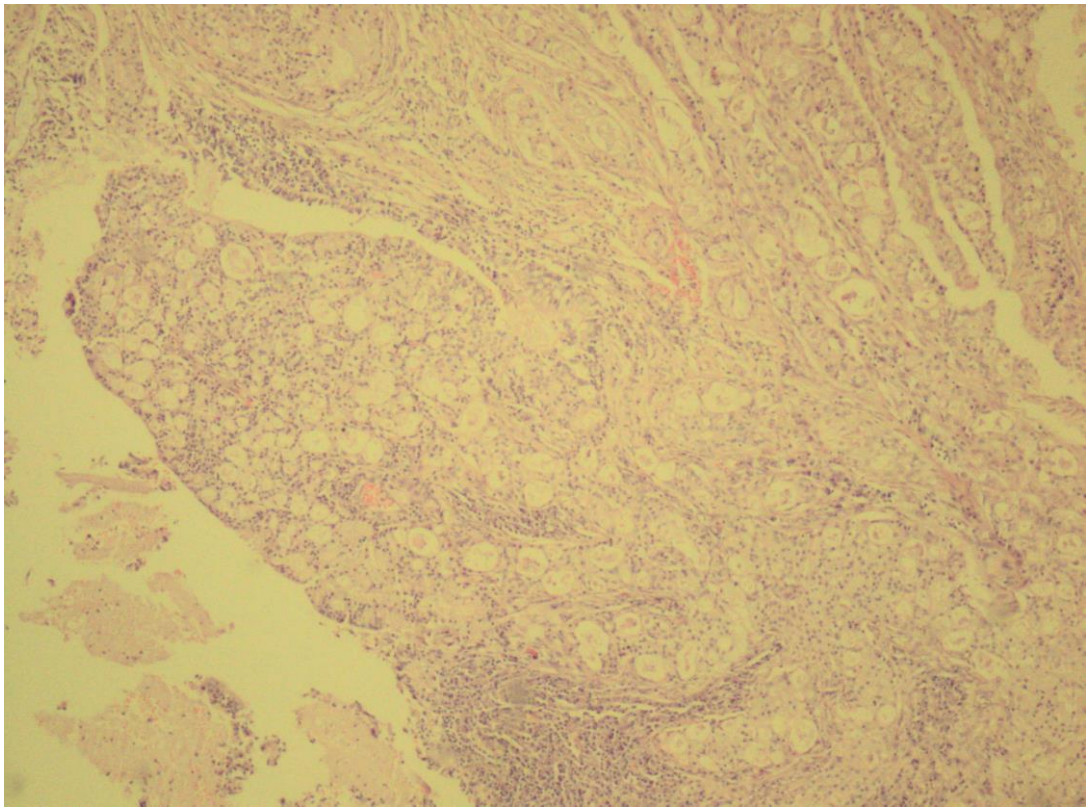


***Figure 9**: Glandular elements in mucoepidermoid carcinoma of the bronchus (H&E) X10*



Discussion

The first two cases ever documented were in 1952 by Smetana et al.[4] and by Liebow et al.[5] respectively. Both authors described the tumours as variants of cylindromas and as a subgroup of adenomas. These cases were mentioned as part of a series of pathological reports on lung lesions.

Mucoepidermoid carcinoma and adenoid cystic carcinoma both arise from salivary gland epithelial tissue. These tumours are more likely to arise in the upper third of the trachea contrary to squamous cell carcinoma that usually arises in the distal trachea however the two cases we are describing here were rare distal adenocystic carcinomas. It is even much rarer for these malignancies to occur in main stem bronchi as described in our cases.[6]

They present in younger patients irrespective of smoking habits. The symptoms may be very non-specific and varied. Our cases presented with cough and distal infections however the literature describes cases presenting with chest pain, shortness of breath, hoarseness, hyponatraemia and incidental findings in asymptomatic patients. Therefore these young patients may be easily under-investigated and on average 12 months would have elapsed from the first symptoms to the diagnosis.[7] In our cases the time to diagnosis was 18 and 10 months respectively conforming to that of other cases.

The tumour arises from bronchial glands and is made up of sheets of uniform cells containing glandular lumina. These tumours are identical to salivary gland tumours. Differentiating it from the more common ovarian or pancreatic mucinous cystic neoplasms may be possible with immunohistochemistry, as the pulmonary type is positive for CK7 and CK20.

It is mostly a low-grade, slow-growing tumour that spreads along the submucosa of the trachea or bronchus beyond that which is macroscopically apparent.[8] This explains the increased rates of positive margins, as occurred in one of our cases. Despite this, there is significant benefit in resecting tumours even if adequate margins cannot be achieved as the slow-growing nature of the tumour and the palliation provided by postoperative radiotherapy may result in long-term control.[9] Despite the response to radiotherapy and chemotherapy, surgical resection is the best way to achieve complete cure. The delay in diagnosis, for reasons mentioned above, will compromise the possibility of achieving complete resection. Local invasion beyond the airway is possible but rather than invading mediastinal structures it will push them aside. Local lymph node spread is also possible but less frequent than metastatic spread to the lungs or other distant organs. There is a rare subtype of these low-grade tumours that is highly malignant (grade III) and is prone to early metastatic spread and rapid local recurrence if margins are not clear.[10]

Chest x-ray may sometimes show the tumour,[11] however the gold standard imaging modality is CT scan. Using high resolution CT (HRCT) one can estimate the extent of airway involvement as well as the degree of airway obstruction and distal collapse and infection. Spiral CT with 3D reconstructions will help plan the extent of resection. MRI is not often used but may provide more information on longitudinal extension and on mediastinal infiltration. Lung function tests will clearly show airway obstruction with a flattened flow-volume loop, reduced forced expiratory volume in one second (FEV1) and a reduced peak expiratory flow rate (PEFR). These findings are not reversed with bronchodilators. Bronchoscopy is essential in diagnosing the type of tumour both visually and histologically. Biopsies of these tumours may be hazardous when in the trachea due to acute airway obstruction and bleeding. In our case both lesions were in the main bronchi or branches thereof and therefore biopsies could be performed safely.

Complete surgical resection is the only cure. Chemotherapy and radiotherapy may only play a role in low-grade tumours and will only offer prolongation of lifespan.[12] The type of resection depends greatly on the location of the tumours. The more common tracheal tumours require resection of the airway with primary anastomosis if sufficient length of trachea is available. Novel techniques are being perfected such as neotracheal reconstruction using free forearm full thickness flaps with autologous costal cartilage strips or even tracheal transplantation. However for lesions in more distal airways, such as the ones presented here, resection of the airway with lung salvage is not possible and lobectomy needs to be performed. Gao & Urbanski reviewed 66 cases operated for primary mucinous cystic neoplasms occurring in bronchi and all were treated with lobectomy, segmentectomy or wedge resection with good results.[8] Tumours located in main bronchi, as in one of the cases discussed here,

are amenable to sleeve resections in order to avoid pneumonectomy. As far back as 1980 Breyer *et al*. reported 5 cases operated for mucoepidermoid carcinoma; one underwent lobectomy, another tracheal resection with primary anastomosis and the other 3 received sleeve resections with primary re-anastomosis of the main bronchi.[13]

Even with treatment the 10-year survival is quoted at 53% for low-grade and 39% for high grade.[14] Even with complete resection 5-year survival is 80% for low grade and 31% in the rarer high grade.[12] Interestingly in those with complete surgical resection the 5-year and 10-year survival rates are identical. As in the case of our patients the one with complete surgical resection is well at 9 years whereas the one with positive margins died after 5 years. Local recurrence can occur many years after surgery. The main prognostic factor is lymph node involvement on intraoperative sampling and this should be routinely performed. Therefore these patients require long-term follow-up postoperatively.

Besides the larger case series mentioned above several other small series have been published. Nine case reports of 1 to 3 cases were reviewed and summarised in table 1.

In 1987, Yousem and Hochholzer described 58 cases taken from the Pulmonary and Mediastinal Pathology Registry, Washington between 1960 and 1986. 45 had low-grade tumours with an average age of 34.8 years. Submucosal infiltration was noted in 40 cases. All were resected surgically and one suffered lymph node metastasis, the rest remained disease free. High-grade tumours were present in 13 patients with an average age of 44.5 years. Overall 50% were smokers. All patients but one underwent surgical resection. That one patient was treated with radiotherapy only. Lymph node metastasis was present in 2 cases and both died of the disease, another 3 patients died of widespread metastasis. One patient had local recurrence, which was re-resected and survived.[15]

Table 1*: Series of case reports of patients with mucinous cystadenocarcinoma*

Author	Year	No. of Cases	Age	Presenting features	Surgery	Outcome in months (m)
Raza et al[16]	2009	1	67	Hyponatraemia	Unfit for surgery	n/a
Wynveen et al[1]	2008	1	75	Incidental finding	Lobectomy	Disease free at 24m
Hironori et al[17]	2003	1	42	Incidental finding	Lobectomy	Disease free at 24m
Moran et al[18]	2003	2	48, 61	Dyspnoea, Chest pain	Non-anatomical resections	Disease free at 12m Disease free at 12m
Jesse et al[19]	1984	1	66	Productive cough	Pneumonectomy	n/a
Klacsmann et al[20]	1979	2	39, 52	Cough, Incidental finding	Lobectomy, pneumonectomy	Disease free at 24m Disease free at 24m
Trentini et al [21]	1972	1	25	Dyspnoea, haemoptysis	Sleeve resection (+ve margins)	Died at 3m
Heilbrunn et al[22]	1972	3	22, 59, 60	Pneumonia, hoarseness, chest pain	Lobectomy, (+ve margins) radiotherapy,	Disease free at 6m Died at 24m Died at 12m
Kitada et al[11]	2011	1	60	Incidental finding	VATS lobectomy	Disease free at 9m

n/a = not available

Comparable to the literature our patients were young, average age of 31 years, and both were non-smokers. Smoking is not directly linked to these tumours and neither are environmental pollutants, however the link with lung cancers is present and therefore some influence may be present. Our patients lived in different parts of the island, one in a central town and the other by the sea. Both our patients are male but the literature shows no gender differences in prevalence.[23] They both presented with recurrent chest infections and both were potentially under investigated initially as commonly

occurs. Bronchoscopy gave plenty of visual information but histologically was ineffective. Both cases were of low-grade tumour and had not metastasised to lymph nodes or distant organs at the time of surgery. As discussed above the slow growing nature of this tumour created situations were positive margins were tolerated and local control was achieved with radiotherapy.[9] Our cases show the different outcome in cases with incomplete resection and hopefully encourage others to be more aggressive in achieving clear margins with more advanced techniques of sleeve resections and transplantation. Nonetheless even with positive margins our first case survived for over 5 years (3 years of disease free survival) and that is the reason why a long period of follow-up was essential before reporting these cases.

Learning Points

- Mucinous cystadencarcinomas are rare but highly malignant.
- They occur in patients who would be considered low risk; young patients who are non-smokers.
- They are asymptomatic or present with recurrent chest infections due to major airway obstruction.
- Chest x-ray and even CT may be misleading if infection obscures the tumour.
- A high index of suspicion is required; especially when a young healthy individual is getting recurrent pneumonia. Close follow-up is essential following infection to detect tumour that might have been hidden by infection.
- Early diagnosis and complete surgical resection offers a better chance of cure and therefore a respiratory physician should be consulted early for bronchoscopy and, if needed, the patient is then referred to a thoracic surgeon.

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