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Sepsis – where are we up to?

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It is quite common that we read about novel infections. We are all aware about the mortality secondary to ST elevation Myocardial Infarction which stands at around 8%. Meanwhile, sepsis is an old enemy that still kills many of our patients across the board. Mortality has remained high despite advances in pathobiology due to its complexity and heterogeneity with up to 10% for sepsis going up to 40% for septic shock.

Considerable changes in the 2001 definitions of Sepsis were published in the third international consensus definitions for sepsis and septic shock (Sepsis-3). The old definitions including SIRS (Systemic inflammatory response syndrome), Severe Sepsis and Septic Shock were found to be lacking in sensitivity and specificity while being too lax to allow consistency in gathering data. By using electronic health record data from patients admitted with infection it was possible to retrospectively evaluate the best tools to screen for sepsis *in patients with suspected infection* while aiming for simplicity.

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The management of sepsis remains essentially unchanged. The key is early recognition and treatment, as organ dysfunction can escalate quite rapidly and become potentially irreversible, with a sharp rise in mortality. The last update of the guidelines is from the 2015 Surviving Sepsis Campaign. This is neatly presented in two essential care bundles, the first within 3 hours and the second within 6 hours. The initial bundle includes the measuring of Lactate, administration of 30ml/Kg of crystalloid and appropriate broad spectrum antibiotics after taking blood cultures. Subsequently the patient should be reassessed for perfusion and volume status within 3 hours with repeat lactate adding vasopressors if deemed necessary and aiming for Mean Arterial Pressure (MAP) of >65mmHg. It is important to note that early central venous access has been removed from these care bundles as it has not been shown to add significant benefit.

The Sequential Organ Failure Assessment (SOFA) score was chosen for use in the intensive care setting with an increase of 2 or more points from baseline in a patient with suspected infection defining sepsis. This score needs only the commonly available clinical and laboratory data - platelet count, serum creatinine, GCS, arterial oxygen concentration, serum bilirubin and MAP. These can be easily calculated for every patient at this level of care. The tool chosen for use on the wards and prehospital settings is the quick SOFA (qSOFA) score that is simply 2 or more of: decrease in Glasgow Coma Scale (GCS) to below 15, respiratory rate above 22 breaths per minute and/ or a drop in systolic blood pressure below 100mmHg. The use of SIRS criteria such as fever, neutrophilia and tachycardia complements these tools in helping recognise suspected infection but are considered an adaptive response to infection rather than heralding sepsis. It is noted also that blood lactate has been omitted from these screening tools as it did not add much to their sensitivity or specificity. It remains however an essential tool for assessing perfusion and guiding therapy.

The updated definitions and clinical assessment tools may offer the advantage of earlier recognition of those at risk of sepsis though they are still being prospectively evaluated. The clear and specific definitions will provide better consistency for clinical trials and epidemiologic studies.

The use of these scores coupled with the early recognition and management of such a common pathology is essential in obtaining a better outcome in our patients. Furthermore these outcomes can be obtained without the need of many significant new resources.

Recommended Reading

1. Sepsis definitions and scoring systems: http://jamanetwork.com/journals/jama/fullarticle/2492881.
2. The 2015 update of the Surviving Sepsis campaign guidelines: https://www.sccm.org/Documents/SSC-Guidelines.pdf.

Cover Picture:
'To boldly go'
Oil on canvas with palette knife
By Victor Grech

Victor Grech is a consultant paediatrician with a special interest in paediatric cardiology. He has a PhD in this field and another in science fiction. He is the editor of the journals Images in Paediatric Cardiology and the Malta Medical Journals and co-chairs HUMS, the Humanities, Medicine and Sciences Programme at the University of Malta.

Original Article

Cardiac arrest recognition and telephone CPR by emergency medical dispatchers

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Abstract

Introduction: Emergency Medical Service (EMS) systems annually encounters about 275 000 out-of-hospital cardiac arrest (OHCA) patients in Europe and approximately 420,000 cases in the United States.[1] Survival rates have been reported to be poor with approximately 10% survival to hospital discharge.[2] The chance of surviving from an OHCA is highly associated with Emergency Medical Dispatchers' (EMD) recognition of cardiac arrest, early bystander cardiopulmonary resuscitation (CPR), and early defibrillation.[3-6]

Method: This study was a simulation based study. All emergency nurses who were eligible by training to answer 112 calls and activate the EMS were included in this study. The simulations were run by two experienced ED nurses who followed predefined scripts. The two key questions that the authors were after included ascertaining patient responsiveness and breathing status. EMDs who offered telephone assisted CPR (tCPR) were noted and observed.

Results: The mean percentage recognition of out of hospital cardiac arrest by the Maltese EMDs was 67%. 28% of EMDs who recognized cardiac arrest asked both questions regarding patient's responsiveness and breathing whilst only 8% of EMDs who did not recognize cardiac arrest asked both questions. The mean percentage of telephone assisted CPR was 58%.

Conclusion: When compared to other European countries, OHCA recognition by Maltese EMDs needs to improve. However, given that the local EMDs have no formal guidelines or algorithms for their use during 112 calls, results are encouraging to say the least especially in telephone assisted CPR. With education and simulation training, these numbers should improve

Key Words

Emergency Medical Services, Emergency Medical Dispatchers, Out-of-Hospital Cardiac arrest, cardiopulmonary resuscitation, Telephone assisted CPR

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Introduction

Emergency Medical Service (EMS) systems annually encounters about 275 000 out-of-hospital cardiac arrest (OHCA) patients in Europe and approximately 420,000 cases in the United States.[1] Survival rates have been reported to be poor with approximately 10% survival to hospital discharge. [2] The chance of surviving from an OHCA is highly associated with Emergency Medical Dispatchers' (EMD) recognition of cardiac arrest, early bystander cardiopulmonary resuscitation (CPR), and early defibrillation.[3-6] In communities where this chain of survival is strong, survival rates can reach 20% - 40% in witnessed OHCA.[7-8] In Malta the survival to hospital discharge in OHCA is 3% with a rate of bystander CPR at around 38%. [9] Similarly, in the UK the rate of bystander CPR is about 40%.[10] In a study done in Sweden, Hasselqvist *et al*.[11] found that the rate of bystander CPR was 51%.

Decreasing the time to treatment is crucial for improving outcomes in cases of cardiac arrest.[12-13] As stated in American and European guidelines, the most important response measures that currently can be taken outside a hospital setting are recognizing early that a cardiac arrest is occurring, placing an alarm call, performing CPR, and performing defibrillation.[14-15] EMD who take emergency calls play a key role in the performance of bystander CPR prior to the arrival of EMS personnel on the scene.[16-17] EMD instructions for CPR can double the frequency of bystander CPR. [18] The identification of cardiac arrest via telephone, however, is extremely difficult, especially when a collapsed individual has agonal respiration.[6,19–20] Although the ability to recognize OHCA is a challenging task, in certain European countries such as Finland, the capacity to identify OHCA patients has been reported to be as high as 70–83%.[21–23] Recognition of cardiac arrest by the EMD is thus essential, so that telephone assisted CPR (tCPR) and referral to an automated external defibrillator (AED) can be initiated.

There are certain factors which act as barriers in tCPR. The study done by Bang *et al.*[24], showed that tCPR was unlikely if the caller was not at the scene and that the emotional state of the caller influenced initiation of tCPR. In addition to this study, several studies have shown how the emotional state of the caller affected OHCA recognition and precluded tCPR.[25–28] Dealing with callers who are healthcare professionals can also pose a problem. Castren *et al.* [29] described the phenomenon of significantly lower OHCA recognition in professionals than non-professional bystanders, and less use of the algorithm by EMD when dealing with calls from healthcare professionals. The aim of this study was to explore the recognition of OHCA by our local EMD and the frequency of telephone assisted CPR offered to bystanders.

Method

This study was a simulation based study involving two hypothetical 112 calls. Two scenarios involving cardiac arrest victims were chosen from a pool of six common 112 calls that our control room in the Emergency Department at Mater Dei Hospital receive. Scenarios were chosen since we had no access to actual 112 recordings involving cardiac arrest victims. All emergency nurses who were eligible by training to answer 112 calls and activate the EMS were included in this study. The simulations were run by two experienced ED nurses who were not included in the study. Verbal consent for recruitment was obtained from the participants, however, to minimize bias the reason behind these simulations or feedback on the simulation itself was not disclosed to the participants. The simulation was run in english or maltese based on the EMD's preference.

The assessors pretended to be bystanders to a collapsed victim calling the ambulance control room and followed a pre-defined script (*Table 1 – Scenario 1 & table 2 – Scenario 2).* Certain key questions which the authors thought was important to determine OHCA were discussed and determined before the start of the simulation and the assessors were asked to tick certain boxes on the script if these pertinent questions were asked by the participants. The two key questions were:

- to determine patient's response by vocal and/or tactile stimulation and
- Whether the patient is breathing normally.

In addition, during the simulation, note was made on the type of ambulance code dispatched (Red, Orange or Blue – *(Table 3 – Types of Ambulance codes)*) and whether telephone assisted cardio pulmonary resuscitation was offered to bystanders if OHCA was recognized. As a final remark, participants were asked to give their impression on what they were dealing with.

Results

Out of 54 eligible ED nurses, 52 took part in this simulation based study. In Case 1 where you had an unresponsive patient, who is not breathing, 92% (48/52) recognized an out of hospital cardiac arrest. TCPR was started in 75% (36/48) of cases. Eighty-eight percent (88% - 42/48) dispatched a code red and 12% (6/48) dispatched a code orange. Only 8% (4/52) did not recognize an OHCA with 2 code reds and 2 code orange dispatched *(Table 4 - Results Case 1 – Unresponsive not breathing patient).* In Case 2 where you had an unresponsive patient, with agonal breathing, 42% (22/52) recognized an OHCA. TCPR was started in 41% (9/22) of the cases. Seventy-seven percent (77% - 17/22) dispatched a code red and 23% (5/22) dispatched a code orange. Fifty-eight percent (58% - 30/52) did not recognize an OHCA with 10 code reds and 20 code orange dispatched *(Table 5 - Results Case 2 – Unresponsive patient with agonal breathing).*

Table 1: *Scenario 1*

Caller	My father is not feeling well. We need an ambulance urgently!
Dispatcher	What happened?
Caller	He had shortness of breath but now he is not talking!
Dispatcher	**If you call him or stimulate him, does he open his eyes or respond in any way?**
Caller	No
Dispatcher	**Is he breathing?**
Caller	No
Dispatcher	Takes details and address? cardiac arrest – dispatch code red
Dispatcher	***Do you know how to perform CPR?***
Caller	No
Dispatcher	***Place left hand over the centre of the chest and the right hand over the left hand locking both hands together and with the heel of your left hand press hard and fast – 30 compressions. Then give 2 breaths by tilting the head back, pinch the nose and blow twice in mouth.***

Dispatcher impression of case

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Telephone CPR by dispatcher – Y / N

Table 2*: Scenario 2*

Caller	(A lot of shouting) We need an ambulance urgently!
Dispatcher	What happened?
Caller	He's in his chair..... He vomited as well!!!!
Dispatcher	Is he talking to you?
Caller	No!
Dispatcher	**If you call him or stimulate him, does he open his eyes or respond in any way?**
Caller	No
Dispatcher	**Is he breathing?**
Caller	What do you mean?
Dispatcher	**Is he breathing normally?**
Caller	Very shallow and slowly
Dispatcher	Takes details and address? cardiac arrest – dispatch code red
Dispatcher	***Do you know how to perform CPR?***
Caller	***No***
Dispatcher	***Place left hand over the centre of the chest and the right hand over the left hand locking both hands together and with the heel of your left hand press hard and fast – 30 compressions. Then give 2 breaths by tilting the head back, pinch the nose and blow twice in mouth.***

Dispatcher impression of case

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Telephone CPR by dispatcher – Y / N

***Table 3**: Types of Ambulance codes*

Code RED	Ambulance response with **blue lights & siren for potentially life threatening** (Category A) **calls**. The ambulance response is Emergency Nurse led with ambulance support personnel and a doctor may be dispatched as required from health centre or otherwise.
Code ORANGE	Ambulance response with **blue lights & siren as required for urgent but non-life-threatening** (Category B) **calls** which require support by an emergency nurse according to dispatch protocol.
Code BLUE	Ambulance response with **blue lights only for 112** (Category C) **calls which do not require support by an emergency nurse** according to dispatch protocol.

***Table 4:** Results Case 1 – Unresponsive not breathing patient*

Recognition of OHCA	92% (48/52)	Missed OHCA	8% (4/52)
Started tCPR	75% (36/48)	Started tCPR	0
Dispatched code Red	88% (42/48)	Dispatched code Red	50% (2/4)
Dispatched code Orange	12% (6/48)	Dispatched code Orange	50% (2/4)

***Table 5**: Results Case 2 – Unresponsive patient with agonal breathing*

Recognition of OHCA	42% (22/52)	Missed OHCA	58% (30/52)
Started tCPR	41% (9/22)	Started tCPR	0
Dispatched code Red	77% (17/22)	Dispatched code Red	33.3% (10/30)
Dispatched code Orange	23% (5/22)	Dispatched code Orange	66.7% (20/30)

***Table 6**: EMD impressions in unrecognised OHCA*

Cardiac event/MI x8	Hypovolaemia x1
Hypoglycaemia x8	HI x1
Syncope x7	AAA x1
CVA x4	Airway compromise x1
Choking x2	Gastritis x1

***Table 7**: OHCA recognized by EMDs*

Case 1 – unresponsive and not breathing	**Case 2 – unresponsive with agonal breathing**
29% asked both relevant questions (14/48)	27% asked both relevant questions (6/22)
4% asked about responsiveness only (2/48)	0% asked about responsiveness only (0/22)
64.5% asked about breathing only (31/48)	68% asked about breathing only (15/22)
2% did not ask any questions (1/48)	5% did not ask any questions (1/22)
	73% assumed that if the patient is not talking therefore the patient is unresponsive and did not ask for response (16/22)

The mean percentage recognition of out of hospital cardiac arrest by the Maltese EMDs over these two cases was of **67%.** The mean percentage of tCPR over these two cases was of **58%.**

In the unrecognized OHCA over both cases, the impressions that the EMDs gave were mainly myocardial infarctions and hypoglycaemias and syncope. Others included cerebrovascular accidents, choking, hypovolaemia, head injury, ruptured abdominal aorta aneurysm, compromised airway and gastritis *(Table 6* - EMD impressions in unrecognised OHCA*)*.

If one had to look at the two key questions that EMDs had to ask to ascertain cardiac arrest:

Of those who recognized an OHCA (*Table 7 - OHCA recognized by EMDs*):

- 28% asked both relevant questions
- 2% asked about responsiveness only
- 66% asked about breathing only
- 3.5% did not ask any questions

Of those who did not recognize OHCA (*Table 8 - OHCA not recognized by EMDs*):

- 8.5% asked both relevant questions
- 19% asked about responsiveness only
- 51.5% asked about breathing only
- 21% did not ask any questions

Table 8*: OHCA not recognized by EMDs*

Case 1 – unresponsive and not breathing	**Case 2 - unresponsive with agonal breathing**
0% asked both questions (0/4)	17% asked both questions (5/30)
25% asked about responsiveness only (1/4)	13% asked about responsiveness only (4/30)
50% asked about breathing only (2/4)	53% asked about breathing only (16/30)
25% did not ask any questions (1/4)	17% did not ask any questions (5/30)

Discussion

The EMS locally is mainly run by emergency nurses and the EMD is solely run by emergency nurses. To be eligible to practice as an EMD, an emergency nurse needs to have worked for at least 1 year in the emergency department and completed successfully a supervised 10 session training programme on ambulance dispatch and EMS protocols. Currently, local EMDs do not have an official protocol on OHCA recognition. From this study, the mean percentage recognition by EMDs of OHCA was found to be 67%. It is a known fact that the ability to recognize OHCA is a challenging task, but still the capacity to identify OHCA patients in Europe has been reported to be as high as 83%. [22, 24, 30] Moreover the mean percentage of telephone assisted CPR locally was found to be 58%. Kuisma *et al*.[30] showed that although bystander CPR in Finland was 71.3%, only 32.3% of OHCA patients in Finland were given tCPR. In another study from Seoul, South Korea, this number was 24.2%, with only 5.2% of the patients receiving CPR. [16] In another study in Taipei, Ma *et al.* [31] reported that about 33% of OHCA bystanders received tCPR instructions. Considering that at the time of writing local EMDs do not have an official algorithm or guideline on tCPR, this number is very encouraging and shows the awareness Maltese EMDs have on the benefits of tCPR. Various studies have shown that dispatchers are less likely to identify an OHCA if they do not ask about consciousness, do not confirm that a patient's breathing is normal[6, 19], or mistake agonal breathing sounds for normal respiration. [32] In this study, only 28% of EMDs who recognised OHCA asked about consciousness and normal breathing. Most of the EMDs could identify an OHCA by only asking whether the patient is breathing (66%). In contrast, when an OHCA was missed, only 8.5% of EMDs asked about consciousness and normal breathing but consistently a high number of EMD (51.5%) enquired about breathing only. Clegg *et al*.[33] analysed recordings from emergency calls and found that identification of breathing patterns was one of the most difficult and time consuming tasks during OHCA incidents. These results highlight the lack of a structured approach EMDs take when dealing with OHCA calls. The sole reliance on breathing questions especially when confronted with agonal breathing, which is notoriously difficult for lay people to explain, decreases significantly the recognition of OHCA. Successful recognition of OHCA is associated with an assessment of both the patient's consciousness and breathing pattern.[19,34-37]

Fukushima *et al.*[38] showed that laypersons describe agonal respiration in a wide variety of ways such as weak breathing, snoring and wheezing. Since the descriptions of agonal respirations are diverse, it is difficult for dispatchers to distinguish true cardiac arrest at emergency calls. Fukushima *et al.* [38] noted that while 84.2% (96/ 114 cases) of those who were described as 'not breathing' were identified as cardiac arrest and provided CPR instruction, only 27.8% (47/ 169 cases) of those with agonal respiration were identified as cardiac arrest. Along with other previous reports, many cardiac arrest victims with agonal respirations might lose the chance to receive CPR because of the misrecognition of cardiac arrest.[19-20] This is consistent with this study's reported results, with a higher recognition of OHCA (92%) in the unresponsive not breathing patient (Case 1 - 48/52), compared to OHCA recognition of 42% in a case of agonal breathing (Case 2 - 22/52). Other barriers to recognition of OHCA include the caller's description of signs of life, the type of caller, caller's emotional state and inadequate dialogue during the emergency call. In an analysis of emergency calls, Lewis *et al.* [39] found the factors that delayed dispatcher recognition of cardiac arrest were dispatcher-related (asking unnecessary or inappropriate questions), caller-related (emotional state, vague or misleading answers), and call-related (language barriers, time spent moving the patient). In addition, since victims not in cardiac arrest such as stroke can present with abnormal breathing, [40] there are concerns from EMDs about the risk of layperson CPR on non-cardiac arrest victims. [41] Recent studies have shown that the frequency of serious injury on non-cardiac arrest victims by CPR was very low.[42-43] A systematic review and pooled analysis done by Miller *et al.* [44] revealed that the incidence of CPR-associated major thoracic injuries such as aortic laceration, cardiac injury, pneumo/hemothorax or liver injury occur in up to 7 % of cardiac arrest victims. When it comes to unresponsive victims not in cardiac arrest, however, the risk of CPR was extremely low. Previous studies reported that chest compression for those not in cardiac arrest is much less hazardous resulting in chest discomfort or minor rib fractures.[43,45] Considering the high sensitivity and low specificity for abnormal breathing and low risk of chest compression for unresponsive persons not in cardiac arrest, it is suggested that EMS dispatchers can provide CPR instruction assertively and safely for those unresponsive cases with various abnormal breathing patterns described by laypersons.[46]

Recommendations

Our main recommendation is to provide educational programmes and training for dispatchers through protocols and simulation training focusing on communication challenges and identification of breathing patterns. Specific guidelines and algorithms should be made available for EMD use during 112 calls. Targeted simulation and education significantly increased recognition of OHCA and reduced time to first chest compression. In a study by Hardeland *et al.* 289 and 221 calls were included before and after targeted simulation and education respectively. Recognition of cardiac arrest improved from 74% to 89% (p<0.001), and delayed recognition was reduced from 14% to 5% (p=0.001). Agonal respiration continued to challenge dispatchers, but misinterpretation of abnormal breathing decreased from 25% to 8% (p<0.001) of calls. Median time to first chest compression was reduced by 30 seconds (204 vs. 174 seconds, respectively, p=0,039).[47] There is some evidence that a dispatcher's increased exposure to cardiac arrest calls can result in better outcomes for patients. Kuisma *et al.*[32] found an association between the frequency of cardiac arrest calls a dispatcher handled and patient survival rates. For dispatchers who handled fewer than four such calls during their study period, survival to hospital discharge was 22 %; by contrast, when dispatchers took more than nine calls, survival was 39 %.[13] It is plausible that additional opportunities to practice cardiac arrest call-taking, with targeted training on evaluating the need for tCPR, specifically, training on consistent querying of patient consciousness and breathing status, could improve dispatchers' ability to identify suspected cardiac arrest and decrease time to start of tCPR.

Conclusion

When compared to other European countries, OHCA recognition by Maltese EMDs needs to improve. However, given that the local EMDs have no formal guidelines or algorithms for their use during 112 calls, results are encouraging to say the least especially in telephone assisted CPR. With education and simulation training, these numbers

should improve.

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Review Article

Medical or surgical approaches to obesity treatment, or both?

Erica Cini

Abstract

Obesity is a growing concern in the medical profession, particularly due to the co-morbidities that are related to obesity. Various methods have been trialled to manage obesity with varying effects, but can we ever say that one which is better than the other? This article looks at various lifestyle, pharmacological and surgical aspects of the management of obesity and discusses the diverse theories as to why the maintenance of weight loss can be difficult.

Key Words

Obesity, lifestyle, CBT, medication, bariatric surgery

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Obesity is defined as a medical condition in which excessive fat accumulation causes a negative impact on health.[1] It is defined as a Body Mass Index equal or greater to 30. A sustained decrease of 10% initial body weight is effective in reducing co-morbidities.[2] Current guidelines recommend a multi-disciplinary approach for obesity management.[3-4]

Lifestyle approaches include dietary modification and/or exercise/activity prescription and behavioural therapy. Diets can result in 2.1-6.6% weight loss.[5] Lifestyle changes are a long-term commitment and adherence to a diet plan is a big issue and one of the main causes that diets fail.[6] The addition of exercise to the dietary programs, significantly improve weight loss at follow up.[7] Behavioural therapy for obesity management is associated with an 8-10% weight loss. The issue with this intervention is that on discontinuation, the weight was noted to be regained.[8]

The underlying assumption of lifestyle interventions implies that the patient has responsibility to maintain the weight loss. Mark (2006) challenges this view and introduces a proposition that the underlying increase in appetite arises as a direct result of weight loss.[9] Liebel et al.'s study (1995)[10] suggests that weight loss results in a decrease in total energy expenditure, explaining why weight loss maintenance is difficult. An alternative explanation could be secondary to the hormonal changes, such as leptin deficiency[11] and ghrelin secretion, that occur during diet-induced weight loss.[12]

Medication, such as Orlistat a reversible lipase inhibitor and Liragutide a glucagon-like peptide-1, have been used in the treatment of obesity.[13-14] Orlistat is the only medication approved in the paediatric age group.[15] There is no doubt that anti-obesity medication is more effective than placebo in inducing weight loss.[16] However, this still only ranges between 0-7.6% weight loss.[8] Moreover, morbidly obese patients are less likely to respond to pharmacotherapy.[8]

Bariatric surgery has resulted in effective weight loss in morbidly obese patients.[17-18] This is namely offered to adults but recent trends show that it is also becoming a treatment option for adolescents.[19] There are 3 main types of bariatric surgery procedures:

1. Restrictive surgery: This involves a reduction of the stomach size through gastric banding, gastric sleeve or an intra-gastric balloon.
2. Malabsorptive surgeries: This involves re-organisation of the digestive system which impacts on its ability to absorb nutrients - e.g. jejunoileal bypass, duodenal-jejunal bypass or biliopancreatic division.
3. Combination Surgery: This involves a combination of restrictive and malabsorptive surgeries. Examples of this include Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch.

One year on, the results of bariatric surgery are promising with 70 and 68% weight loss with biliopancreatic diversion and gastric bypass respectively and 48% weight loss following gastric banding.[17] Sleeve gastrectomy and Roux-en-Y gastric bypass have better remission rates than those following gastric banding.[20] Sleeve gastrectomy is a simpler procedure and is therefore easier to perform. It is associated with a reduced need of long-term post-operative multi-mineral and multi-vitamin supplementation. If the target weight loss is not achieved, this procedure can be revised.[20] Highest success in seen when such surgery is performed by a bariatric surgery specialist.

Mortality risks and health care cost following bariatric surgery is promising. Mortality is reduced by 89%[21] and health care costs are reduced by 29% at 5 years.[22] This combined with the added advantages of the wholly or partial resolution of diabetes[8] and improvement in the patient's quality of life - rated at 95% improvement,[23] places bariatric surgery as a valuable treatment option. Furthermore, long-term studies indicate sustained weight loss over 14 years, which is promising.[24]

As with all treatments, there is a risk-benefit ratio that needs to be taken into account. Brethauer et al. (2006)[8] phrases this succinctly: "the risks are not trivial, but they are acceptably low" (p. 993). Despite this, these must be explained and clarified to the person undergoing surgery in order to ensure that informed consent is achieved. The main surgical complications include bleeding, anastomotic leaks, wound infection, thromboembolism, anastomotic strictures, marginal ulcers, bowel obstruction and cholelitiasis. Nutritional deficiency (namely iron, calcium, Vitamin B12, Vitamin D) is another post-operative risk factor[25] that can lead to secondary co-morbidities such as secondary hyperparathyroidism. This can be managed by regular nutritional status levels and added supplementation.

The core of obesity management is in a multidisciplinary approach and often one will find that a combination of treatment modalities are used. If obesity is considered as a chronic illness[26] then a chronic disease model of care would be the most effective. This would imply that each individual's needs is assessed repeatedly throughout their care journey and a responsive care plan with the interventions tailored to the patients' needs. Bariatric surgery provides far greater improvement in terms of immediate/long-term and co-morbidity outcomes, particularly in the treatment of morbid obesity[4] and in those with diabetes.[8,20,24]

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Original Article

An assessment on the use of chest imaging in children admitted with viral induced wheeze

Cecil Vella, Elizabeth Muscat

Introduction

Viral induced wheeze in preschool children (children less than 5 years of age) is a common condition encountered by general practitioners and paediatricians worldwide. Martinez et al, in 2005 showed that approximately 25-30% of infants and young children would have at least two episodes of wheezing in early childhood. Approximately 40% will have had an episode of wheeze by the age of 3 years and almost half of them will have had at least one episode of wheezing by the age of six.[1] Bisgaard et al in 2006 showed in a cohort study that nearly 33% of children between the ages of 1 and 5 years suffer from wheezing associated with upper respiratory tract infections.[2] Fortunately, the majority tend to have only transient symptoms which resolve by five to six years of age.[1]

The small anatomy of the bronchi in infants results in higher peripheral airway resistance. Subsequently, respiratory illness will have proportionately greater impact on total airway resistance. In addition, infants have less elastic tissue recoil and fewer collateral airways, making them susceptible to obstruction and atelectasis. The rib cage, trachea, and bronchi are also more compliant in infants and young children. These factors make infants and young children particularly susceptible to wheezing and respiratory distress.[3]

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Aim

Chest radiographs are frequently performed in children presenting with viral induced wheeze. There are no local guidelines on the need for chest x-rays in infants and children presenting with wheezing associated with viral respiratory tract infections. This review was carried out to assess the frequency of chest x-rays performed and the frequency of abnormal x-rays. Chest imaging is usually performed to exclude lower respiratory tract infections. In young children with viral induced wheeze who present with tachypnoea and cough the use of chest imaging should be limited to those patients in whom a lower respiratory tract infection is strongly suspected.

Methodology

All patients, up to five years of age presenting with a diagnosis of viral induced wheeze to the Paediatric Emergency and Admitting (E&A) department at Mater Dei Hospital Malta, between January and December 2016, were included in the review. Infants aged six months or less with a diagnosis of viral bronchiolitis were excluded. Data was collected retrospectively from an admission register. Viral induced wheeze was defined as an episode of wheeze associated with an upper respiratory tract infection in a child less than five years of age. Chest radiographs were reported by a general radiologist.

Results

A total of 210 children were admitted to the general paediatric wards with a diagnosis of viral induced wheeze during the study period. 122 patients (58%) had a chest x-ray performed at the E&A department prior to admission. The commonest indication for performing a chest radiograph was a fever associated with the episode of wheezing. No abnormality was noted or reported in 92 (75%) of chest x-rays taken. 29 patients (25%) had a chest x-ray report ranging from mild peri-bronchial cuffing (86%) to collapse or consolidation

(14%). Peri-bronchial cuffing is a frequent finding on chest radiographs in patients with viral bronchiolitis and bronchitis and does not signify secondary lower respiratory tract infection.

Discussion

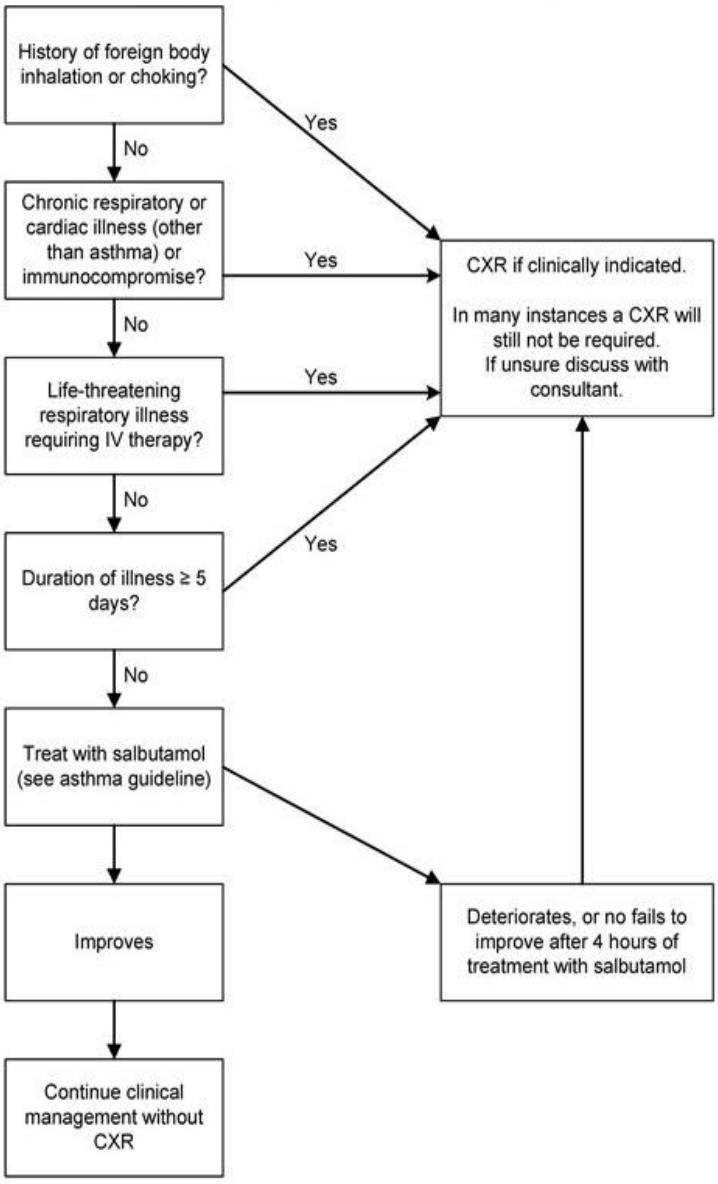
Children with recurrent viral induced wheeze frequently attend the accident and emergency department for nebulized treatment, and occasionally require admission. Chest x-rays are regularly requested, as there are no clear guidelines as to when imaging should be performed. Our review clearly shows that the vast majority of imaging requests are negative. Fever is a common presenting symptom in children with viral associated wheeze and should not be an indication for imaging unless a lower respiratory tract infection is strongly suspected from other signs or symptoms.

Despite its high prevalence, there is a lack of evidence regarding the pathophysiology, treatment and necessary investigations of viral induced wheeze. There is no evidence that chest radiographs help in the diagnosis or treatment of preschool children with acute or recurrent wheezing.[4] Retrospective reviews of chest x-ray use in preschool age wheeze suggested that such investigation did not contribute to the diagnosis or management of the condition.[5] Imaging should only be performed when a concurrent pneumonia is suspected or a suspicion of foreign body aspiration is present. In children with severe wheezing, the presence of subcutaneous emphysema or significant differences in air entry between left and right lungs should alert to the possibility of a pneumothorax and imaging should be performed.

Conclusion

Viral induced wheeze is one of the most common conditions that requires visits to the Paediatric E&A department particularly during the winter months. Chest imaging is frequently requested but does not usually alter the management. We suggest that more attention is given prior to ordering imaging unless significant underlying pulmonary pathology is suspected in the acute phase. Children with frequent and recurrent wheezy episodes may be imaged at a later stage if underlying pulmonary pathology is suspected together with other investigations as required.[6]

Figure 1*: Chest x- ray in children >6 months of age with viral induced wheeze.*



Adapted from: Shepherd M., (2010) 'Chest X-ray in acute wheeze' [5]

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Review Article

Revisiting Parenteral Nutrition-Associated Liver Disease (PNALD)

Edgar Pullicino

Abstract

Parenteral Nutrition-Associated Liver Disease (PNALD) causes progressive cholangitis which can lead to liver failure and cirrhosis especially in infants. Developments in the understanding of its pathogenesis are revisited in the context of the need for guidelines for its safe management and support

Keywords

parenteral nutrition, cholestasis, liver failure, liver fibrosis, jaundice

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Introduction: **PNALD: the perfect storm**

Parenteral Nutrition associated liver disease (PNALD) is characterised by progressive cholestasis associated with a serum conjugated bilirubin above34 umol/l during two consecutive measurements in patients dependent on parenteral nutrition (PN). Fifteen to 40% of adults on long term home PN may also develop PNALD, often in association with intestinal failure. However PNALD has been studied much more intensively in the paediatric age group.

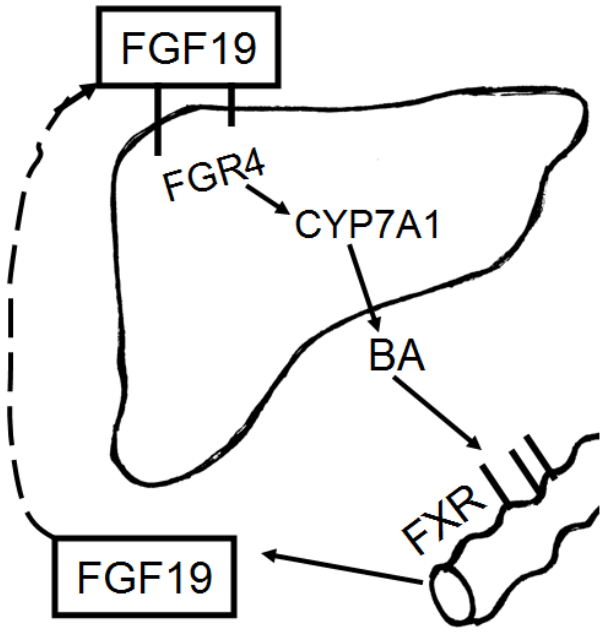
PNALD is commonest and most severe in premature neonates, often in association with the short bowel syndrome (SBS). The incidence of SBS in neonates has been estimated at 24.5 per 100,000 live births. Two thirds of these patients will develop PNALD with a case fatality rate of 37.5%[1]. Histologic evidence of cholestasis is seen within 2 weeks and varying degrees of liver fibrosis within 6 weeks of starting PN.[2] PNALD occurs in up to 70% of such patients during 8-14 weeks of PN [3] and may progress to cirrhosis and fatal liver failure. PNALD is the leading indication for liver/ intestine transplantation in infants.[4] Failure to wean infants onto enteral feeding increases the need for liver and intestinal transplantation. Immature liver enzyme systems, gut mucosal atrophy with loss of hormonal output from the unfed gut, intestinal bacterial translocation, PN component toxicity, and PN-mediated exaggerated inflammatory response creates a "perfect storm" for progression to liver failure. This article revisits the multiple proposed aetiologies and pathogenetic mechanisms which inform proposed therapeutic strategies in PNALD and revisits the evidence-base on how they may impact on the progress of this disease.

The cause of PNALD? : A Crime by omission?

In the search for the aetiology of PNALD, failure or inability to feed the gut is slowly replacing PN-related toxicities on centre-stage as the prime crime, with bile acids (BA) emerging as the main culprit. Healthy subjects economise on

intestinal BA by their ileal reabsorbtion and their subsequent enterohepatic circulation. Bile acids complete the round trip from ileum to liver and back about twice during every meal. Luminal BA, particularly chenodeoxycholic acid (CDCA) act as ligands to, and activate, the nuclear farnesoid X receptor (FXR) in the intestinal epithelium which then releases fibroblast growth factor 19 (FGF 19).[5] FGF 19 reaches the liver via the portal vein, and after binding to fibroblast growth factor 4 receptor (FGFR4) it represses the activity of cholesterol 7 alpha hydroxylase, a rate-limiting enzyme in hepatic BA synthesis (Figure 1). Disruption of the enterohepatic BA circulation by isolation of significant lengths of small intestine from exposure to food and bile leads to unrepressed hepatic BA synthesis which can be corrected by enteral administration of chenodeoxycholic (CDCA) but not Ursodeoxycholic acid (UDCA).[6] Resumption of enteral feeding may also help to restore enterohepatic BA recirculation.

Figure 1: *Bile acids (BA) bind to farnesoid X receptor(FXR) receptor in terminal ileum causing release of fibroblast growth factor 19 (FGF19) which travels through the portal circulation to the liver where it binds to its receptor FGFR4 leading to suppression of cholesterol 7 alpha hydroxylase (CYP7A1), a rate limiting enzyme in bile acid synthesis.*



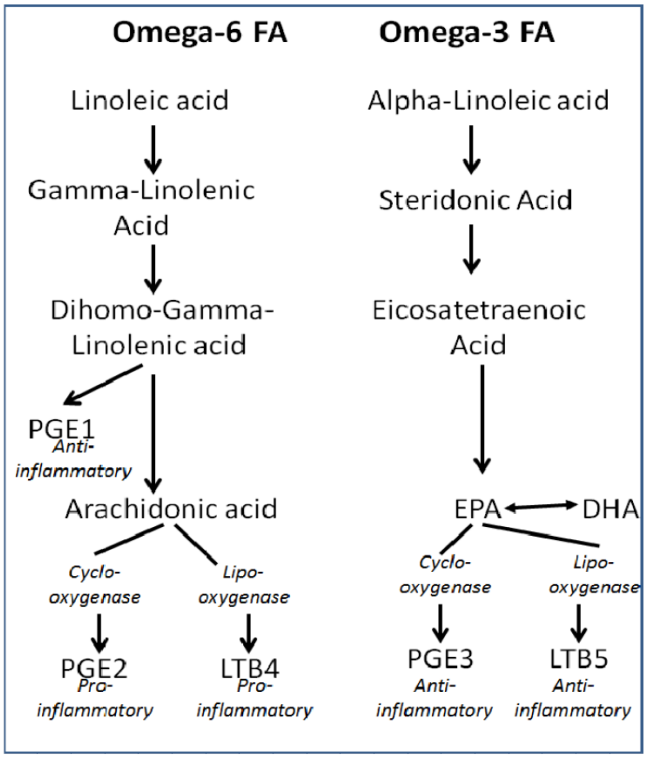
Food and bile acids exert both trophic and incretin effects on the intestinal epithelium through the bile salt-activated G protein-coupled receptor TGR5 which regulates secretion of glucagon-like peptides (GLP) 1 and 2 by intestinal endocrine cells.[7] GLP2 reverses intestinal mucosal atrophy while GLP1 restores the insulin response to food [8] and its deficiency may be partly responsible for glucose intolerance, dyslipidaemia and fatty liver seen in some patients on long term PN.

Gut rest, systemic antibiotics, and mucosal atrophy with low IGA are all potential causes of intestinal dysbiosis. Overgrowth of gram-negative species reminiscent of the dysbiosis observed in the gut of cirrhotic patients[9] is often present in intestinal failure patients. Small intestinal bacterial overgrowth increases gut permeability, allowing translocation of bacteria to the liver where endotoxin disrupts bile acid transport.[10] Here FXR and TGR5 have again been implicated.[7] FXR modulates intestinal epithelial carbonic anhydrase [11] which regulates luminal pH and therefore bacterial levels while TGR5 reduces the expression of cytokines like TNF which mediate liver injury.[12]

Preventing irreversible liver damage: A fishy business?

Infant PN regimens typically infuse 2- 3g/ kg /day of soyabean oil as an intravenous fat emulsion (soya-IVFE) e.g. Intralipid (Fresenius kabi®) containing a high ratio (7:1) of omega-6 to omega-3 polyunsaturated fatty acids (PUFA), both of which compete for the cycloxegenase and lipoxygenase pathways (see figure 2). Omega 6 PUFAs, predominantly Linoleic acid, are metabolized to 2-series prostaglandins e.g. PGE 2-series, and 4-series leucotrienes e.g. LTB4 via the cyclooxygenase and the lipooxygenase pathways respectively. Both LTB4 and PGE2 are proinflammatory and predominate on the antinflammatory effects of PGE1 produced upstream in the same pathway. In contrast omega-3 PUFAs, mainly alpha-linolenic acid, docosahexanoic acid (DHA) and eicosapentaenoic acid (EPA) are precursors of anti-inflammatory mediators such as PGE3 and LTB5 which reduce inflammation. Arachidonic acid exerts some of its proinflammatory effect by activating the nuclear factor kappa B (NF-κB).[13] In contrast omega-3 fatty acids inhibit NF-κB activation via a peroxisome proliferator-activated receptor (PPAR alpha) -dependent pathway. Metabolites of omega-3 PUFA that resolve inflammation such as resolvin have been shown to be hepatoprotective in mice.[14]

***Figure 2**: Omega-6 fatty acids are predominantly metabolized to proinflammtory mediators PGE2 and LFTB4 while omeg-3 fatty acids are predominantly metabolized to anti inflammatory mediators PGE3 and LTB5*



The above contrast between different PUFAs has led to trials of intravenous fish oil-based emulsions (fish-IVFEs) such as Omegaven (Fresenius Kabi®) which has a very low ratio of omega-6 to omega-3 PUFA (1:8) mainly containing EPA and DPA (see figure 2) which modulate PPAR alpha.[7] Fish oils induce more beta-oxidation of fats and reduce lipogenesis thus reducing fat deposition in the liver. Compared to plant oils they do not contain phytosterols and they have a higher content of tocopherol (see below). They still await FDA approval and are only used in the USA on a compassionate basis. At lower doses of IVFA fish-IVFE monotherapy may not meet the infant's requirement for essential fatty acids. This has prompted the manufacture of mixed lipid emulsions such as SMOFlipid (Fresenius Kabi®) (30% soyabean oil, 30% MCT, 25% olive oil, 15% fish oil).

Soya and other plant- based emulsions also contain phytosterols which are potentially hepatotoxic. PN abolishes the protective limitation on the absorbtion of these plant sterols normally afforded by the enteral route.[15] El kasmi et al, in a model of PNALD in parenterally fed mice with intestinal injury, showed that parenteral fish oils prevented liver damage and hepatic macrophage activation by soya-IVFEs, and that stigmaserol promotes cholestasis and Kuppfer cell activation by suppressing canalicular bile transport expression through antagonism of FXR nuclear receptors.

Soya IVFEs are also relatively deficient in alpha-tocopherol which is a crucial antioxidant in the PNALD scenario. The dyslipidaemia and hepatic steatosis which characterise both PNALD and non-alcoholic fatty liver are associated with the accumulation of long chain fatty acids (LCFA) in hepatocytes. Disposal of LCFA by hepatic mitochondrial B-oxidation is overwhelmed and rescue pathways such as peroxisomal beta-oxidation and microsomal omega-oxidation are activated. [16] All this extra oxidative stress produces excess reactive oxygen species (ROS) such as superoxide which risks overwhelming the enzymes such as catalase, superoxide dismutase and the antioxidants such as tocopherol and glutathione which scavenge free radicals, which would otherwise damage hepatocytes through lipid peroxidation of their membranes . The burden on tocopherol is further exaggerated by oxidative stress secondary to bile duct damage. During PNALD vitamin E comes to the rescue, not only by means of its classical antioxidant function, but also specifically by activating xenobiotic receptors such as the pregnane X receptor (PXR)[17] that wake up auxiliary scavenging by conjugation, sulphation and by cytochrome P450.

Coping with PNALD: too many verdicts awaited?

Treatment of PNALD aims to halt the hepatic fibroinflammatory reaction before it becomes irreversible. Early and repeated attempts to introduce enteral feeding are of utmost importance as many of the above aetiologies will be reversed. Enteral feeding should be carefully advanced and PN reduced. [18]Even non-advanced minimal enteral feeding will help to reverse gut atrophy and restore gut hormonal responses (see Table 1). Non-nutritive sucking will help to prepare the infant for later feeding. Measures that maximize the length and function of residual viable bowel should be put in place including serial transverse enteroplasty (STEP) procedures if appropriate. When enteral feeding is contraindicated e.g. early phase of necrotizing enterocolitis the following alternative

strategies have been studied in the literature:

IVFE restriction: Restriction of soya IVFE to 1g/kg/day from the start of PN has been associated with significant reduction in PNALD but data on detailed nutritional parameters and essential fatty acid status have not been studied.

Cyclic PN: The use of cyclic PN throughout the intravenous feeding period has not been adequately studied in the literature[18] and may be poorly tolerated in acutely ill neonates

Fish IVFE: Following the first use of fish-IVFE in a teenager with soy-allergy in 2005[19] fish-IVFE administration has been reported in infants with PNALD to reverse cholestasis, reduce PN duration, reduce mortality, reduce transplant rates and to stabilize but not to prevent the early onset of liver fibrosis.[18] Most of these studies used historical PNALD cohorts treated with soy-IVFE. A metanalysis in 2012 by Seida et al[20] of five randomised controlled (RCT) trials and 3 prospective cohort studies reported insufficiency of high quality data to support the use of fish-IVFEs in children. The study was heterogeneous and fish-IVFEs were not always the sole source of lipid in the study group. A more recent metanalysis[21] of two RCTs (Jadad score of 5) and five non-randomized studies of fish-IVFE as the sole or partial source of intravenous lipids concluded that IVFEs are effective in reversing but not in preventing PNAC in neonates requiring prolonged nutritional support.

Mixed IVFEs: The low content of essential fatty acids (EFAs) in fish-IVFEs has caused at least a theoretical concern that infants with fat malabsorbtion receiving low volumes of PN may develop EFA deficiency. This has prompted the combined use of soy and fish-based IVFEs (mixedIVFEs) such a s SMOF (Fresenius Kabi®: soya, olive and fish oils, medium chain triglycerides) which have been reported to be of benefit in PNALD but not adequately compared to fish-IVFEs.[16] Research in this area is limited by the fact that fish oil- based IVFEs are still awaiting approval by the FDA in the USA. The ASPEN 2014 guidelines failed to recommend the use of fish/mixed IVFEs pending further trials.[22]

Prevention of sepsis: Judicious use of antibiotics and other measures that prevent peritoneal, catheter-related and other sources of sepsis are expected to improve PNALD outcome. The ASPEN 2014 guidelines on PNALD failed to recommend ethanol locks of central PN catheters due to unresolved concerns regarding risks of thrombosis and disrupted catheter integrity.[22]

UDCA: A retrospective cohort study[23] reported that cholestasis took longer to resolve in 64 neonates treated with UDCA than in controls. This is not surprising since UDCA has minimum affinity to FXR as compared with the natural bile acid CDCA. The ASPEN 2014 guidelines were unable to recommend UDCA treatment due to insufficient evidence in four analysed reports.

Table 1: *Strategies that may limit liver failure in PNALD*

Strategy	Comment
Start minimal enteral feeding early	Reverses gut atrophy, may be poorly tolerated
Advance enteral feeding	Restores bile acid homeostasis
Restrict calories administered as IVFE	Other calorie sources need high infusion volumes
Administer cyclic TPN	Faster volume infusion may be poorly tolerated
Use fish based IVFE	Theoretical risk of essential fatty acid deficiency
Use mixed IVFEs	Not adequately compared to fish-IVFEs
Treat with ursodeoxycholic acid	Poor efficacy as only weak FXR agonist
Treat with potent FXR agonist (Obeticholic acid)	Favourable reports from phase 2 clinical trial

FXR agonists: The above-mentioned ability of CDCA, a natural human BA to bind to the farnesoid X receptor (FXR) has prompted the synthesis of a 6α-ethyl derivative of CDCA called Obeticholic acid (OCA), a first-in-class drug that binds to FXR with 100 times more potency than CDCA.[24] Phase II human clinical trials have shown that OCA is safe, and effective in reducing liver inflammation and fibrosis in type 2diabetes and non-alcoholic fatty liver (NAFLD), and in reducing serum alkaline phosphatase, a surrogate marker of risk of fibrotic progression in primary biliary cirrhosis. In addition to its ability to modulate liver regeneration after liver injury, FRX is expressed in human stellate cells in which it reduces expression of extracellular matrix proteins with a potential to reverse hepatic fibrosis which has already been demonstrated in rats.[25] FRX agonist was more effective than CDCA in a piglet model of PNALD.[26]

Conclusion

Available management strategies improve cholangitis in some PNALD scenarios but do not prevent fibrosis which appears to start very early in the course of the condition and which is often self-perpetuating through stellate cell activation. Of the two outcomes, prevention of fibrosis is likely to be more challenging than reversal of cholangitis. Perhaps the most effective strategy is to start enteral feeding early and to advance feeds while tapering PN. However, the patients with the highest mortality (typically premature / low birthweight, septic, and with acute enteric pathology such as necrotizing enterocolitis) will not tolerate this approach. The emerging challenge is to discover agents which will restore enteric hormonal, cytokine, and metabolic homeostatic responses during the early phase of intestinal failure. These could be bile acids,[27] gut hormones or agonists to the various gut receptors such as FRX. Intense research in the field of NAFLD- cirrhosis is likely to discover new FRX agonist in other drug classes e.g. the nonsteroidal FXR agonist GW4064.[28] Comprehensive guidelines to manage and prevent PNALD should be based on RCTs that control for gestational age, birthweight, type and dose of IVFE, and length of residual functional small intestine with clearly defined endpoints, such as the prevention or reversal of liver fibrosis and the reversal of cholangitis.

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Original Article

Local survival outcomes in metastatic renal cell carcinoma

Gerald Busuttil, Joseph Attard, David Farrugia, John Sciberras, Stephen Mattocks, Karl German, Patrick Zammit

Abstract

A quarter of patients who develop renal cell carcinoma will have metastatic disease at presentation. The role of cytoreductive surgery in these patients is a topic of debate.

The aim of this study was to analyse survival outcomes of patients treated in Malta who did and did not receive a nephrectomy.

Data was gathered retrospectively from the Malta Cancer Registry and Mortality Data at the Department of Health Information, records of multidisciplinary team meetings held within the urology department at Mater Dei Hospital, hospital imaging and patient records. Data gathered included: patient demographics, date of diagnosis, TNM staging, tumour histology, Fuhrman grade, time to treatment and modality of treatment.

Exclusions included:

- Localized disease relapsing after surgery
- Non-renal cell histological subtypes
- Presence of metastasis at diagnosis not certain
- Concomitant primary tumours

77 patients diagnosed over 5 years between 04.03.2005 and 13.2.2009 were included. The age at presentation ranged from 30 to 88 years, with a median age of 67 years. 11 were incidental findings and 47 were symptomatic. The most prevalent symptoms were abdominal pain and gross haematuria.

Five-year cancer specific survival in patients who received a nephrectomy was significantly better at 65%, compared to patients who did not undergo surgery (32%) P value <0.05, CI 95%. These results where compared favourably with SEER data outcomes

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Keywords

Renal cell cancer, cytoreductive nephrectomy, cancer specific survival.

Introduction

Renal cell carcinoma (RCC) is one of the ten most common malignancy in both men and women. The American Cancer Society estimates that 62,700 new cases of renal cell carcinoma (39,650 in

men and 23,050 in women) will be diagnosed in 2016 in the USA, with 14,240 people (9,240 men and 5,000 women) dying from this disease. [1] Local data from the European Cancer Observatory for 2012 cites a Maltese incidence and mortality from RCC of 57 and 27 per 100, 000 population (age standardised) respectively.[2]

The incidence of RCC has increased over the last decade, and although there has been a definitive stage migration to low stage disease, this being attributed to increasing use of cross sectional imaging and incidental diagnosis of RCC , up to 25% of cases are metastatic at diagnosis.[3] The prognosis in these cases is dismal with the American Joint Committee on Cancer quoting only an 8% five-year overall survival for stage IV RCC.[4]

Faced with these poor outcomes and paucity of oncological alternative therapies, the urological community investigated the benefit of cytoreductive nephrectomy in the presence of distant metastases, and showed a survival benefit when combined with interferon therapy.[5-6] More recently, the development of targeted therapies has led to the substitution of interferon therapy by these drugs in view of their superior efficacy and adverse effect profile. [7] In the local setting, sunitinib (Sutent®), a tyrosine kinase inhibitor, has been the sole agent in use for many years, although more recently everolimus has also been introduced as second line therapy for patients progressing on sunitinib or first line therapy for poor prognosis metastatic cases. The role of cytoreductive nephrectomy in combination with these new agents is still a controversial issue.[8-9]

In this retrospective, non-randomised observational study we compared survival outcomes in a local population of patients with metastatic renal cell carcinoma receiving Sunitinib treatment with or without nephrectomy.

Method

The aims of this study where to analyse cancer specific survival in patients with metastatic RCC in Mater Dei Hospital Urology Unit, compare outcomes between patients having cytoreductive nephrectomy with patients receiving oncological management with sunitinib monotherapy, analyse survival in patients stratified according to MSKCC prognostic groups, and compare these results with National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program database outcomes.

All patients presenting with metastatic renal cell carcinoma to the Urology Unit at Mater Dei Hospital between 04.03.2005 and 13.2.2009 were retrospectively considered for inclusion. The diagnosis was based on radiological investigations. Histological confirmation of cancer types was not mandatory in patients who did not receive a nephrectomy in view of the high diagnostic specificity and sensitivity of cross sectional imaging in the diagnosis of solid or complex cystic renal masses.

Patients were excluded if their primary disease was a non-renal cell kidney cancer, the presence of distant metastases was in doubt at time of diagnosis, the metastatic progression occurred in the context of localised disease at diagnosis that relapsed at a distant site following surgery with curative intent or the presence of other primary tumours prior to or following diagnosis of renal cell cancer. Patients were also excluded if they did not receive at least one dose of sunitinib adjuvant therapy.

Data was gathered retrospectively from the Malta Cancer Registry and Mortality Data at the Department of Health Information, records of multidisciplinary team meetings held within the Urology department at Mater Dei Hospital, hospital imaging and patient records. Mortality data was corroborated by death certification data obtained from the National Cancer Registry to minimise inaccuracy.

Data gathered included: patient demographics, date of diagnosis, TNM staging, tumour histology, Fuhrman grade, time to treatment and modality of treatment.

The patients were risk stratified according to the revised Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups for metastatic renal cancer. These represent a revision of the original Motzer criteria, [10] updated by Heng *et al* in 2009 to reflect the introduction of targeted therapy in the management of metastatic kidney cancer.[11] These have been externally validated in an independent large series.[12]

The prognostic factors that are included in this model include; Karnofsky performance score <80%, time to treatment <1 year, anaemia, hypercalcaemia, neutrophilia and thrombocytosis. Patients were risk stratified into three groups as follows; good prognosis if 0 factors, intermediate prognosis if 1 – 2 factors, poor prognosis if >2

factors as in the original paper by Heng *et al*.

Long term cancer specific survival outcome was compared between two patient groups, those who received cytoreductive nephrectomy and those who did not. Cancer specific survival was also investigated in a subgroup analysis per MSKCC prognostic group stratification. Survival between the two groups was documented via Kaplan Meier survival curves, with a p value of <0.05 taken to represent significance.

Results

77 patients satisfied the inclusion criteria. The study period selected allowed for the analysis of long term survival data in this patient population, with the shortest assessment interval (to death or ongoing survival) being 3.5 years. The majority of patients enrolled were male, 53, as opposed to 24 female patients. The median age at presentation was 67 years with a range from 30 years to 88 years.

14% of cases were incidental diagnoses, whilst 61% of patients presented with symptoms related to local or metastatic disease. In 25% of cases the method of presentation was not available. The most common symptoms at presentation where abdominal or loin pain (21%), gross haematuria (19%), lung (13%) or spinal (11%) symptoms. (Figure 1).

The vast majority of cases presented with T3 or T4 tumours at diagnosis, as per UICC International Union Against Cancer, 7th Edition.[13] (Figure 2). 47 were clinically node negative at presentation, whilst 29 cases had radiological evidence of regional lymph node metastases, lymph node status was not documented in one patient. All patients had radiological evidence of distant metastases at time of diagnosis, thus being classified as TNM stage IV.

***Figure 1**: Presenting features in symptomatic cases*

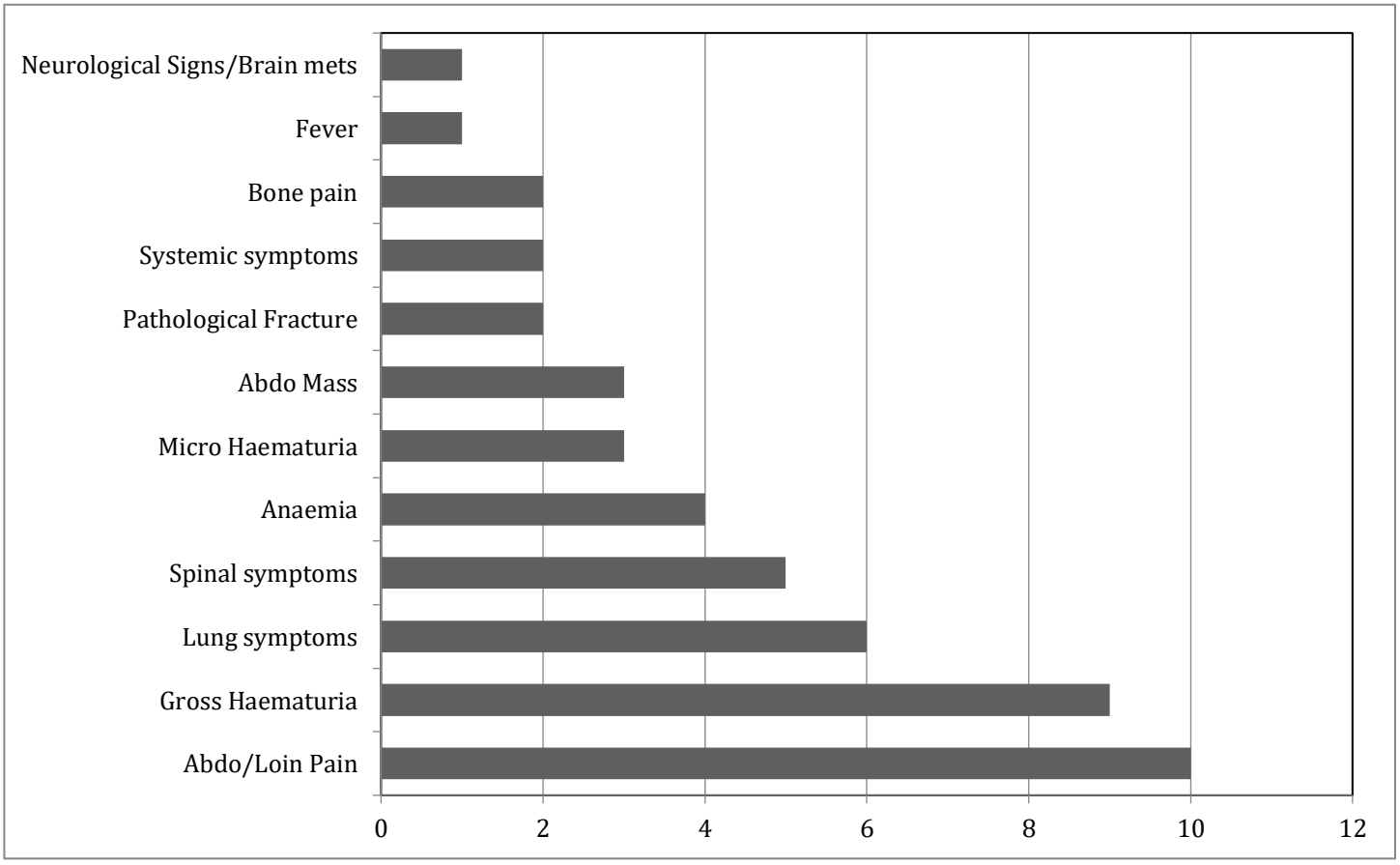


***Figure 2**: Local Tumour stage at diagnosis.*

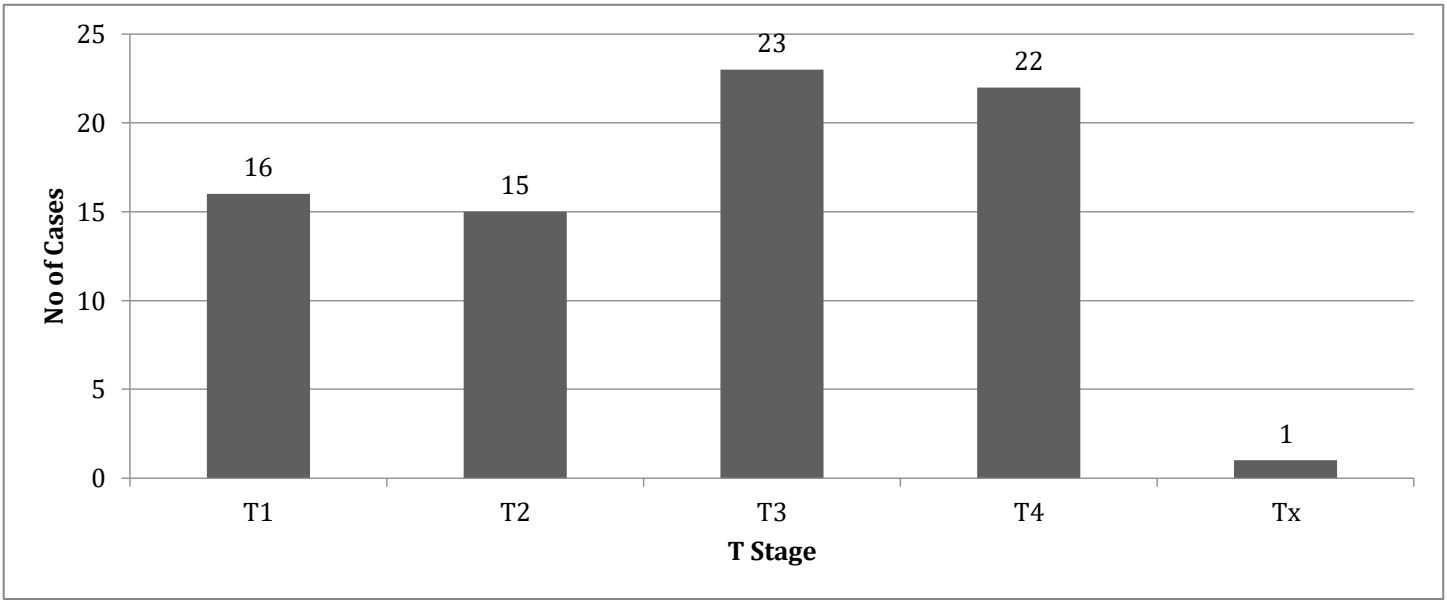


***Figure 3**: Kaplan Meier Curves showing improved cancer survival in nephrectomy group.*

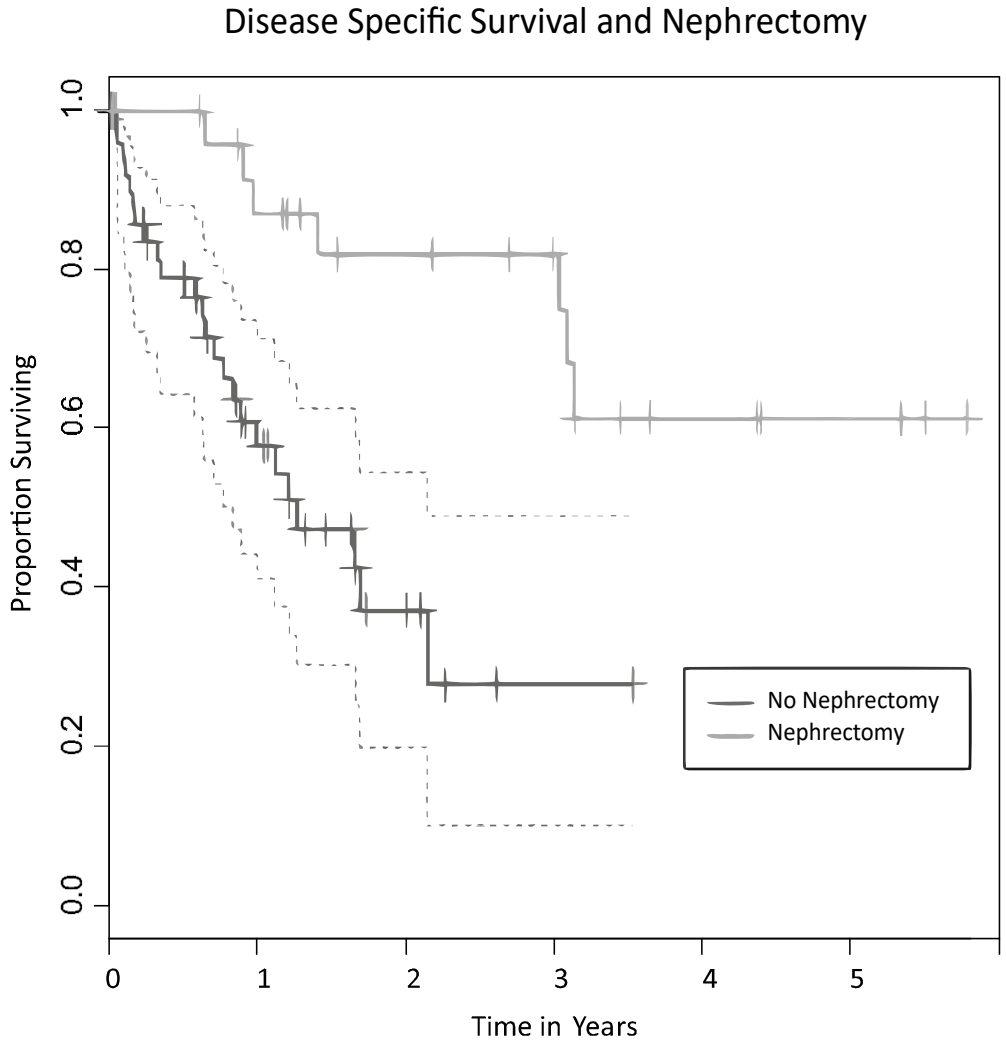
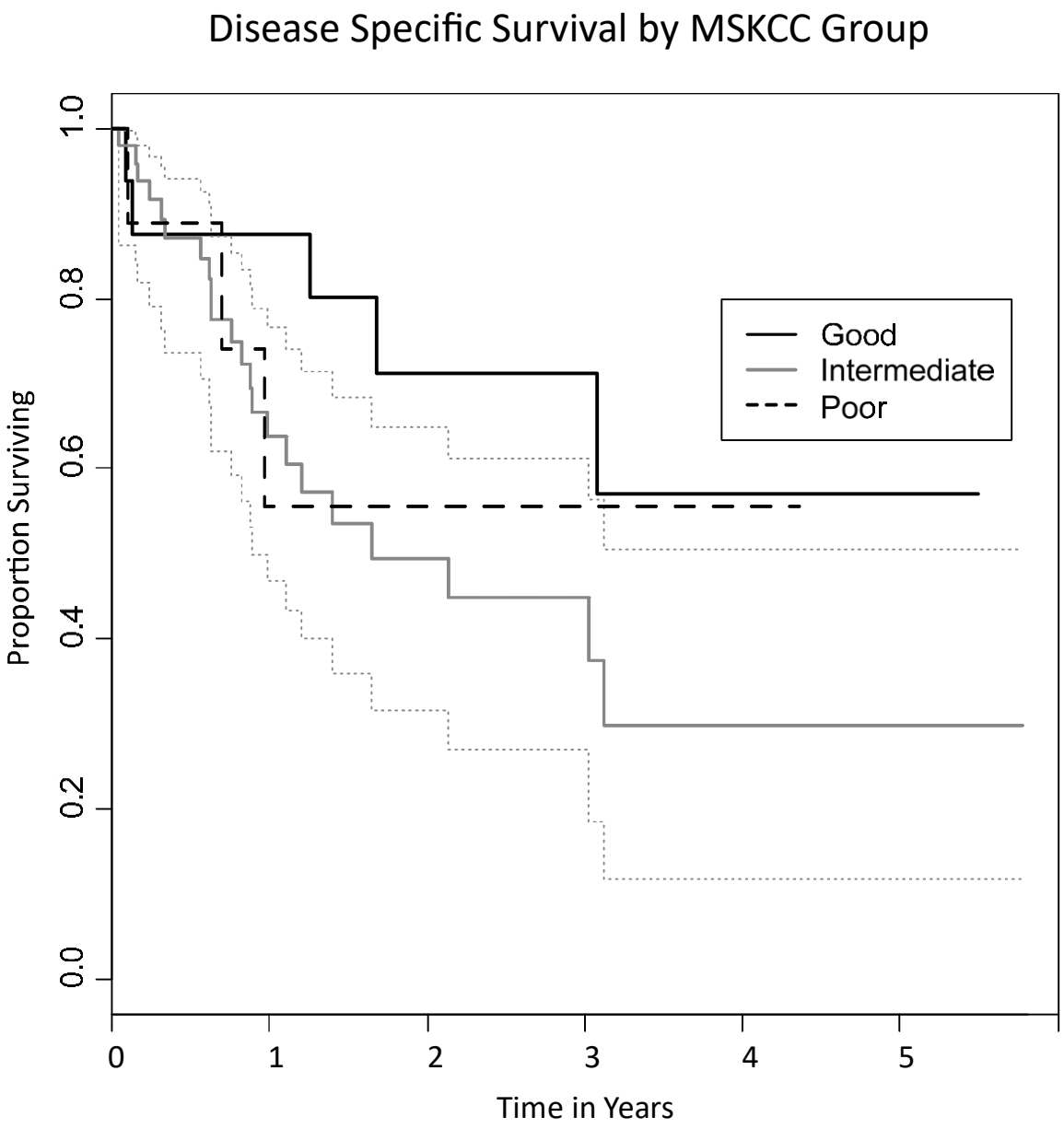


***Figure 4**: Kaplan Meier curve for MSKCC good, intermediate and poor prognosis groups*



Histological subtype was known in only 40% in view of the fact that most patients did not have radical surgery or biopsy of metastatic lesions but diagnosis relied on imaging. In those patients where histology subtype was known, clear cell RCC was the predominant type in keeping with RCC epidemiological patterns (clear cell 27 cases, papillary 2 cases, chromophobe 2 cases).

25 (32.5%) patients underwent cytoreductive open radical nephrectomy during the study period. 45 patients (58%) had passed away at time of censoring (18/8/2015).

Five-year specific survival in patients who received a nephrectomy was significantly better at 65%, compared to patients who did not undergo surgery (32%) P value <0.05, CI 95% as showing in Figure 3.

Subgroup analysis with stratification per MSKCC prognostic risk factors was performed. 17 patients were classified as good prognosis, 49 were considered to have an intermediate prognosis and 10 patients were included into the poor prognosis group. Insufficient data prevented accurate stratification in one patient who was excluded from subgroup analysis.

Five-year survival data showed a significant

difference between the good prognosis and intermediate prognosis groups with a trend towards a poorer outcome in the intermediate group. The poor prognosis group had better long term outcome than the intermediate group, however this is likely to represent an outlying and unrepresentative result in view of the small number of patients in this group. These results are showed graphically in Figure 4.

These results where compared favourably with SEER data outcomes,[15-16] as shown in Tables 1 and 2.

Discussion

In modern day urology, almost one third of clear cell renal cell cancers (the predominant histological subtype of renal cell carcinoma) present with locally advanced or metastatic disease.[17] Given the relatively high incidence of renal cell cancer, the urological and oncological community is faced with the difficult management of a significant number of patients whose disease has a poor long term outcome despite aggressive multimodality management with surgery and an ever expanding armamentarium of targeted therapies.

This aggressive approach is still a topic of debate, as only retrospective non-comparative data exists for cytoreductive nephrectomy in combination with modern targeted therapies. The pioneering work which explored the role of radical surgery in the presence of metastatic disease was performed in the era of immunotherapy prior to the introduction of targeted biological agents. A meta-analysis of these studies, published in the *Lancet Oncology* in 2014, did show an increased long term survival in patients treated with surgery and immunotherapy compared to patients who received immunotherapy alone.[18]

***Table 1**: Cancer specific survival for local patient cohort compared to SEER database data one, two and three years.*

	Malta (2005-2009)		**SEER Database (2006-2009)**	
	Nephrectomy	No Nephrectomy	Nephrectomy	No Nephrectomy
1 year	75.2%	51.2%	70.6%	45.1%
2 years	71%	34.3%	52.2%	27.9%
3 years	65.3%	26.8%	41.7%	21.7%

***Table 2:** Cancer specific survival statistics at 5 years, local and US data.*

MSKCC Prognosis	**Malta (2005-2009)**	**SEER Database (2006-2009)**
Good	57%	36.2%
Intermediate	32%	25.1%
Poor	54%	9.1%

***Table 3**: Published literature investigating role of cytoreductive nephrectomy in combination with targeted therapies in the setting of metastatic renal cell cancer.*

Study (period studied)	Patients, n; CN, no CN	Median OS with CN, months	Median OS without CN, months	Statistically significant patient dispositions in favour of CN ($p \leq 0.001$ to $p < 0.05$)
Retrospective, multi-institutional (2004–2008); Choueiri et al., 2011 [20]	314; 201, 113	19.8	9.4	• Younger age • Better KPS • One metastatic site • Less calcium
Retrospective, SEER (1993–2010); Conti et al., 2014 [21]	20 104; 6915, 13 189	19	4	• Younger age • Male • White
Retrospective, IMDC (2005–2013); Heng et al., 2014 [9]	1658; 982, 676	20.6	9.6	• Better IMDC risk • Less non–clear cell RCC • Fewer bone metastases • Fewer liver metastases
Retrospective, multi-institutional (2006–2011); Bamias et al., 2014 [22]	186; 109, 18	23.9	9.0	• Younger age • Better PS • Less neutrophilia • Lower LDH
Retrospective, SEER (2005–2009); Abern et al., 2014 [23]	2382; 1521, 861	20	6	• Younger age • Male • White
Retrospective, SEER non-clear cell RCC only (2000–2009); Aizer et al., 2014 [24]	591; 377, 214	14	6	• Younger age • Male • White
Retrospective, multi-institutional (1999–2009); Mathieu et al., 2015 [25]	351; 298, 53	38.1	16.4	• Better MSKCC risk • Better ECOG score
Retrospective population-based registry, propensity score matching (2008–2010); De Groot et al, in press [26]	227; 74, 151	17.9	8.8	• T stage <T3/T4 • One metastatic site • Fewer bone metastases
Retrospective, National Cancer Data Base, treated with targeted therapy (2006–2013); Hanna et al, in press [27]	15 390; 5374, 10 016	17.1	7.7	• Younger age • Privately insured • Academic centre • Lower T stage • cN0

Recently this treatment paradigm was adopted by urologists and oncologists and applied to metastatic patients who are treated with targeted therapies which have replaced immunotherapy in modern practice. The evidence base for this approach is not extensive, with no randomised controlled trials to support such an approach to date. Whilst awaiting the results of two randomised trials that are designed to end to this debate, CARMENA (ClinicalTrials.gov identifier NCT00930033) and SURTIME (ClinicalTrials.gov identifier NCT01099423), the European Association of Urology recommends surgery in highly selected patients with good performance status, large primary tumours and low metastatic volume.[17,19]

This approach to metastatic renal cell cancer introduces a heavy selection bias with retrospective studies, with fitter patients with less aggressive disease receiving surgery, whilst those who have a poorer performance status or heavy metastatic load receiving oncological treatment as monotherapy. This inherent flaw cannot obviate the fact that all the retrospective studies published to date have shown an overall survival advantage with surgery in addition to biological agents. (Table 3).

This trend is also evident in our cohort of local patients in which patients who received a nephrectomy had a better long term cancer specific survival than those patients who did not. This is the most important take home message obtained from this retrospective review.

Subgroup analysis with patient stratified according to MSKCC prognostic groups showed some unexpected results with the poor prognosis group of patients doing better than the intermediate risk group. This can probably be attributed to the small number of patients in this group which has resulted in a surprising good outcome.

Compared to SEER data the outcomes in our local cohort of patients compare favourably or significantly better, in all three risk groups but especially in the subgroup who underwent nephrectomy. Again, the vastly superior outcome in the poor prognosis group should not be taken as a true reflection of clinical outcomes in this very small group of patients as already discussed.

The primary tumour accounted for >90% of tumour burden in 55 patients (71.4%), this is an important point as it is likely that a cytoreductive nephrectomy would benefit patients who have most of their tumour mass limited to the kidney. 50 patients (65%) presented with metastases above the diaphragm, this is also relevant as some authorities would not offer debulking nephrectomy in patients with disease above the diaphragm as this is thought to be a very poor prognostic factor with limited benefit being obtained with a surgical approach.[14]

Being the only urology unit in the country, follow up is mostly complete with no patients lost to follow up because of migration. Patients were followed up for an adequate period of > 5 years as is mandatory in oncology studies where survival is the outcome.

Limitations include those inherent to a retrospective audit, including incomplete data, reliance on potentially inaccurate medical notes and bias. Data on overall survival is not presented, and this could reflect real life outcomes in a more meaningful way than cancer specific survival.

Conclusions

Cytoreductive nephrectomy in the presence of metastatic renal cell cancer does seem to offer a survival advantage as demonstrated in this study and other retrospective non-randomised trials. The results from two ongoing large multi-centre randomised controlled studies which are addressing this issue are eagerly awaited.

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Surgical case report of uterine leiomyosarcoma metastasising to the pancreas resected by enucleation

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Abstract

A 64-year old lady presented with worsening abdominal pain, vomiting and constipation. She had diffuse abdominal tenderness with peritonism, requiring an emergency laparotomy as a result of a perforated sigmoid tumour. An incidental hard lump was identified on the anterior surface of the pancreas and was removed by enucleation. It was later diagnosed as metastatic leiomyosarcoma based on histology and from her history of uterine malignancy. No recurrence is reported up to this day.

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Uterine leiomyosarcomas are aggressive malignant tumours with a high predisposition to metastasis, commonly to the lungs, liver, brain and bone. Metastasis to the pancreas is a rare occurrence and considered highly unusual, which can typically present with non-specific symptoms and signs. Imaging can pick up a pancreatic lesion and a radiologically-guided FNA as a pre-operative attempt is acceptable in order to differentiate the lesion before undertaking any major surgery. However, in view of only a few case reports found in the literature, surgical management of pancreatic metastases is not clearly defined with a questionable long-term prognosis. Most cases are managed by elective radical excision with good result.

Review of the literature shows other more radical surgical approaches were used. This is the first report of metastatic uterine leiomyosarcoma to the pancreas being managed by enucleation, with a successful follow-up and no recurrence.

Keywords

Uterine leiomyosarcoma**,** Pancreatic metastasis**,** Emergency surgery**,** Enucleation**,** Malignancy

Presentation of case

A 64-year old lady has a past history of high-grade uterine leiomyosarcoma for which she had undergone total abdominal hysterectomy & bilateral salpingo-oophorectomy three years prior to this presentation. At operation, no obvious metastases were noted and it was confirmed as confined to uterine wall. Following surgery, the patient underwent radiotherapy.

In August 2015, the patient presented with a 1-week history of worsening abdominal pain associated with nausea and vomiting, weight loss and anorexia. She also admitted to passing small amounts of loose stools with a 10-day history of constipation. On examination, she had diffuse

abdominal tenderness with lower abdominal peritonism. Blood investigations revealed a normocytic, normochromic anemia, leukocytosis, neutrophilia, thrombocytosis and hypoalbuminemia. An initial Computed Tomography (CT) scan showed thickening with perforation of the rectum and two lung lesions were noted measuring 0.4 and 0.6cm in the right lung base. She was taken for emergency laparotomy and a Hartmann's procedure was performed. A loop of small bowel invaded by the tumour (which also had palpable lymph nodes in its mesentery) was resected and side-to-side ileal anastamosis was done. The anterior wall of the lesser sac (i.e. the gastro-colic ligament) was opened and a hard lump was noted on the anterior aspect of the pancreas. This was locally removed by enucleation and local haemostasis achieved. No further abdominal deposits were noted.

Gross morphological assessment of the lump removed from the anterior aspect of the pancreas showed a firm nodule measuring 24mm x 20mm x 16mm. On sectioning, it had a white whorled cut surface. Histology of the lesion showed the appearance of a spindle cell tumour with marked nuclear pleiomorphism and bizarre nuclei, with brisk mitotic activity, adjacent to normal pancreatic tissue. The tumour cells resulted as smooth muscle actin (SMA), desmin and myosin positive on immunohistochemistry, consistent with a diagnosis of leiomyosarcoma *(Figure 1 & 2)*.

Figure 1*: (H&E x400 magnification). Spindle cell tumour with a fascicular arrangement, showing marked pleiomorphism and numerous bizarre giant cells. The histology of the lesion is identical to that of the uterine leiomyosarcoma diagnosed in the same patient three years prior during hysterectomy.*

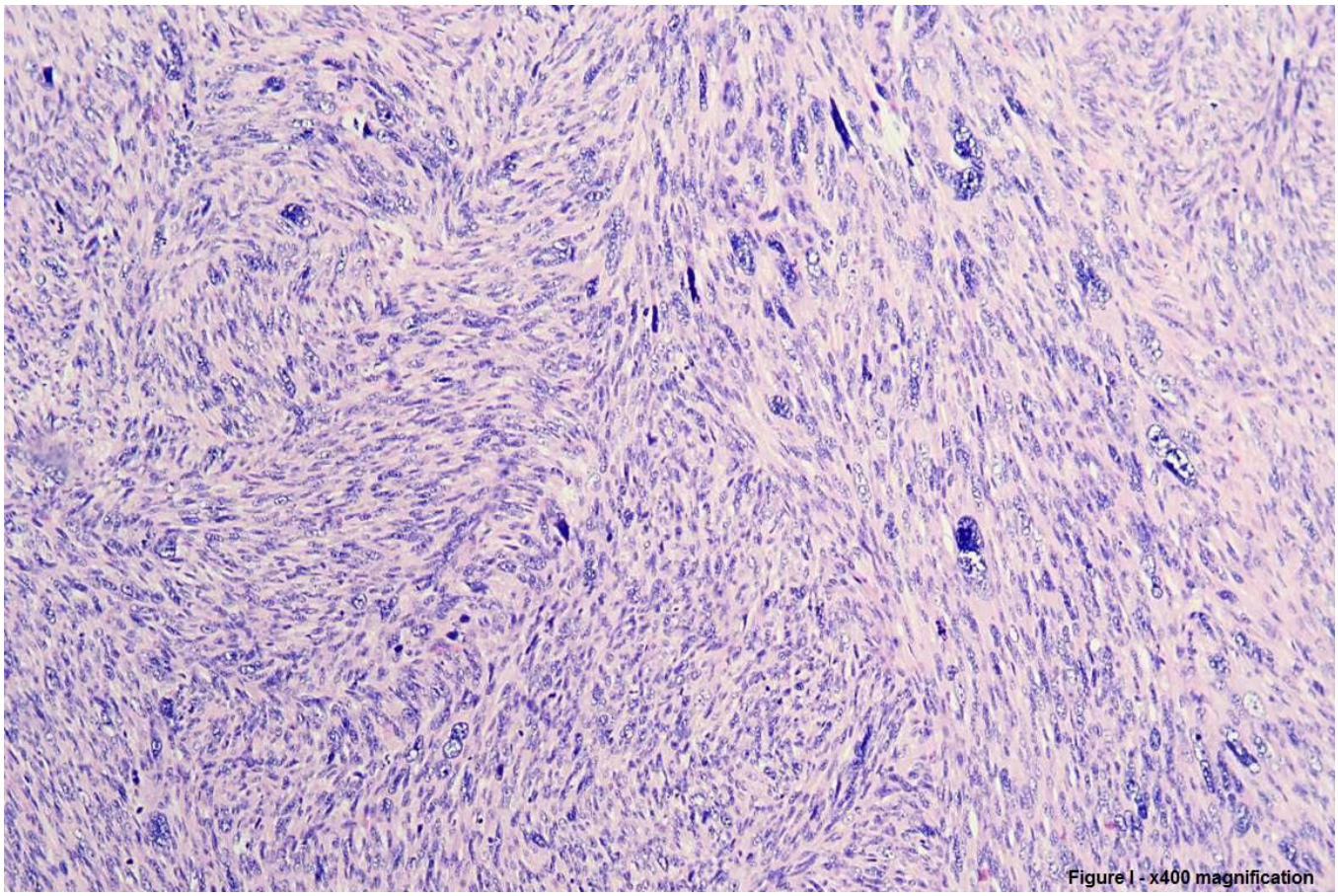
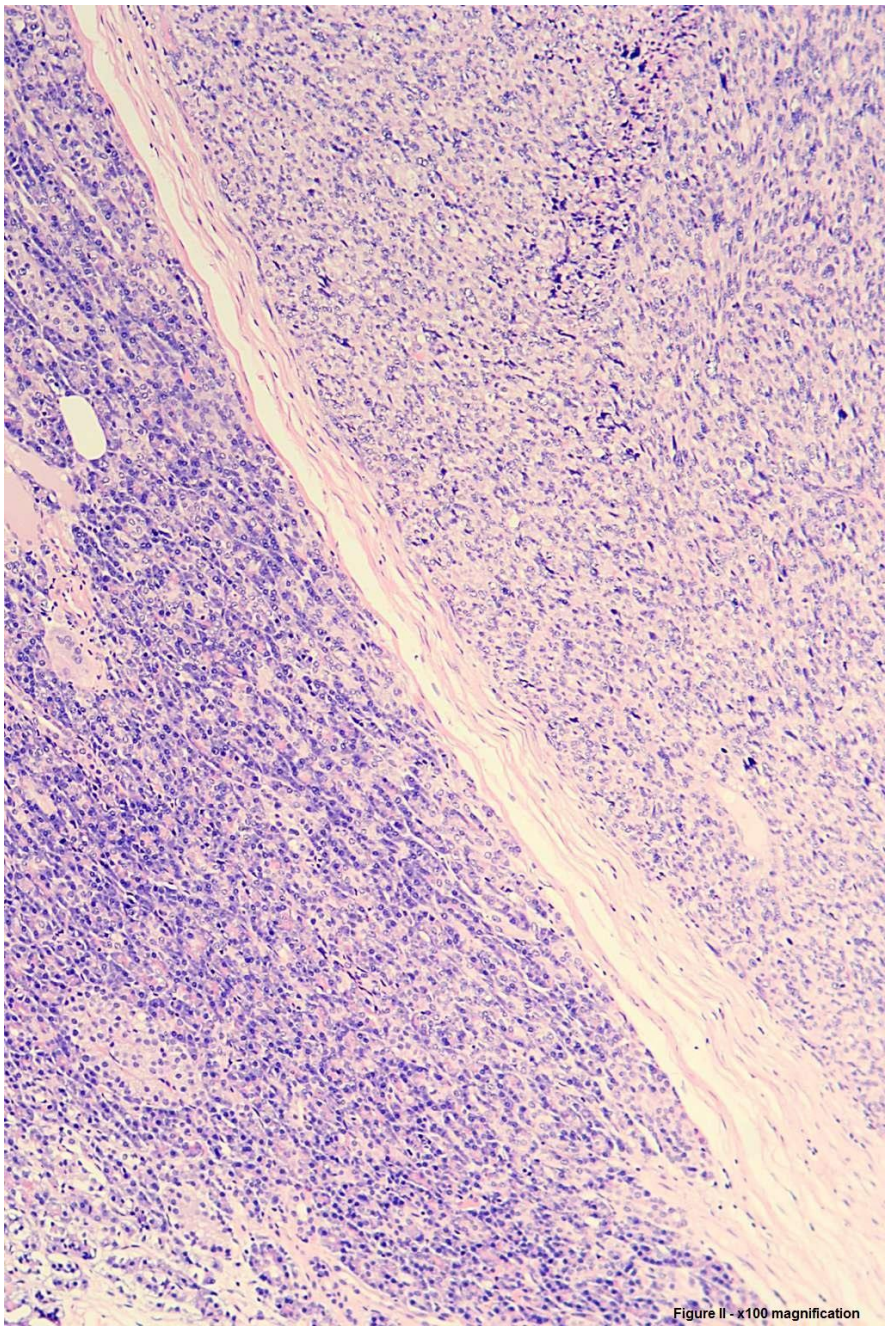


***Figure 2**: (H&E x100 magnification) A thin fibrous capsule separates the leiomyosarcoma in the top right half of the image from the normal pancreatic tissue in the bottom left corner, which allowed the lesion to be locally excised out.*



The intestinal specimens on the other hand showed metastatic intestinal adenocarcinoma over small bowel mesentery, together with moderately-to-poorly differentiated intestinal adenocarcinoma in the large bowel, reaching the radial margin. Significantly enlarged lymph node metastases and perinodal infiltration (11 out of 20 lymph nodes positive for metastasis) were also present (pT4b N2b M1).

During a multi-disciplinary discussion with the pathologist and oncologist, it was agreed that the patient was too frail to undergo further radical surgery to address the pancreas and was continued to be followed-up from the intestinal adenocarcinoma point of view.

Discussion

Uterine leiomyosarcoma is a malignant tumour arising from the myometrial smooth muscle.

It has an aggressive course which requires extensive therapy, necessitating total abdominal hysterectomy with bilateral salpingo-oophorectomy together with regular follow-up in view of its high risk of recurrence. The most common sites of metastasis include the lung, kidney and the liver. [1-2] Apart from the uterus, leiomyosarcomas can also arise from the ovaries, veins, spermatic cord, intestine, retroperitoneum and soft tissue. [3]

Leiomyosarcomas to the pancreas may present as large cystic lesions on imaging. They can be easily mistaken for a pancreatic pseudocyst rather than a malignant lesion. However, the latter are usually more prevalent in men and with a history of gallstones or pancreatitis. [4] In this particular case, the patient is a female with no relevant past history of gallstones or pancreatitis. Moreover, one must keep in mind her past gynaecological history of uterine leiomyosarcoma.

The pancreas is an uncommon site for metastasis to occur, even more so for metastatic leiomyosarcoma of the uterus which is considered as a rare occurrence. Only a few cases have been reported in the literature. Autopsy studies by Nakamura *et al.* have shown that the most common pancreatic secondary tumours are carcinomas, specifically adenocarcinomas. The stomach is the most common primary tumour site, followed by the lung and extra-hepatic bile duct.[5] On the other hand, Adsay *et al.* suggested that lung cancer is the most common source of metastasis to the pancreas. [6]

In the literature such metastatic lesions are typically diagnosed on routine follow-up CT scans, and then excised during elective surgery. They had resorted to radical operations, including pancreaticoduodenectomy, distal pancreatectomy, segmental resection and if not possible to preserve pancreatic tissue, total pancreatectomy has also been reported. In this article, we reviewed a case report where the lesion was noted during emergency surgery and resected by enucleation.

Macroscopically, these lesions show a white whorled surface. Microscopically, they are characterised by interlacing spindle-shaped cells. The mitotic count would give an indication of the level of aggressiveness of the tumour. Other features to look out for include cellularity, degree of atypia and pleiomorphism and presence of myofibrils.[7-8] It is believed that leiomyosarcomas of the pancreas arise from smooth muscle of the pancreatic blood vessels or pancreatic ducts. [9]

In view of lack of standardised guidelines for the management of pancreatic metastases, one must use clinical judgement after taking into consideration the patient's co-morbidities and discuss it in a multi-disciplinary setting. A wide negative resection margin during surgery would ensure complete excision and increase the chances of survival and quality of life. [10] In this particular case, a less radical approach of removing the tumour by enucleation was adopted, and to date, no further recurrence has been reported.

Conclusion

Review of the literature shows other more radical surgical approaches were used. This is the first report of metastatic uterine leiomyosarcoma to the pancreas being managed by enucleation, with a successful follow-up and no recurrence.

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