Ulster Medical Society

Thursday 4 November 2010
Junior Doctors' Prize Evening

Professor Margaret Cupples:

Can I say good evening and welcome to our third meeting of our series of Ulster Medical Society meetings, and I'm delighted to see so many young people in the audience this evening, and we hope that this might encourage you to come back to future meetings in the year, that's great, I can see some heads nodding, because we do like to see the youth help to keep us stimulated in our learning together as we go through our medical practice, and we're very glad see older members here as well, because I think that everyone learns from sharing their experiences.

Now, I'm not going to say very much more except that I would like to congratulate all of the people who have made submissions, which have been selected for either presentation in the posters outside or for the six oral presentations which we're about to hear.

There were almost 60 submissions; we selected 23, so it was by no means an automatic passage to be here tonight. And there are some certificates for all those who were successful in getting here tonight to present something, so if you collect it after the meeting that would be good, you can add that to your CV.

Without further ado I think I would like to ask our first speaker to come forward, Jared Ahmad, and just to say that's there eight minutes allowed for each presentation and a couple of minutes afterwards for questions, and we're going to stick quite strictly to time. Thank you.

Dr Jared Ahmad:

Good evening, Madam President, ladies and gentlemen. In the next eight minutes I'll present original research that was carried out and developed, biomarkers of Barrett's oesophagus. In section one, I'll present a little background of the project, later in section two, I'll present development of the biomarkers.

The incidence of oesophageal adenocarcinoma has increased dramatically in the last two decades and the Barrett's oesophagus is recognised to be the most established risk factor for the development of adenocarcinoma. The diagnosis of Barrett's oesophagus has increased in the UK in recent years and this may translate into the observed increased incidence of adenocarcinoma. Barrett's affects 2% of the adult population in the west, oesophageal adenocarcinoma is the most important complication of this condition with a life-time risk of 5% in men and 3% in women. Once the diagnosis is made the patient is entered into a surveillance programme and an annual risk of developing carcinoma based from 0.4% in the US to 1% in the UK annually.

It is suggested that development of adenocarcinoma in Barrett's oesophagus is likely to follow a sequence from metaplasia to low grade dysplasia, high grade dysplasia and oesophageal cancer, and this model provides the unique opportunity for us to identify dysplasia quite early, and institute appropriate treatment to improve the outcomes.

Madam President, as you can see, oesophageal adenocarcinoma is quite a nasty disease with five year survival for stage four disease is between 0 and 7%. On the other hand, if [mucosal resection?] is carried out for Barrett's oesophagus with high grade dysplasia, it is considered a curative resection, and the five year survival for [?] disease is up to 90%, so surveillance is very, very important in these cases. Presently surveillance of Barrett's oesophagus hinges on regular ODGs and biopsies. It is cumbersome, not 100% sensitive, it's not very cost effective and logically it poses a dilemma to even [the astutest of gastroenterologists?] when they are having to diagnose dysplasia in the background of inflamed oesophagus.

So can we do any better, is there any alternative? The answer would be in the development of biomarkers. A biomarker is a biochemical feature that can be used to measure the progress for disease. An ideal biomarker would confirm the presence or absence of dysplasia, or adenocarcinoma, in the background of Barrett's oesophagus and its comparative expression could predict the disease progression. This biomarker would ideally be absent or weak in benign cases, moderately over-expressed in cases of low grade dysplasia, and strongly over-expressed in high grade dysplasia and adenocarcinoma.

With this background, Madam President, we started a research project that was lab based and the aims were to investigate the expression of three novel biomarkers in tissue sections of Barrett's oesophagus, low grade dysplasia and adenocarcinoma, and to evaluate their potential to differentiate between benign, dysplastic and malignant Barrett's tissue.

A brief introduction of the biomarkers being used in this project, the first one was P504S, that is alpha-methylacyl-CoA racemase. It is an established biomarker for prostate adenocarcinoma, and previously only two small bio-studies have investigated this biomarker and they have shown some promise about the sensitivity of this biomarker. CD133 is a cancer stem cell biomarker, it is suggested that CD133 expression in colorectal cancer is an independent prognostic marker and correlates well with [?] survival. CD133 has not been investigated before in adenocarcinoma or Barrett's oesophagus. The third biomarker was TWIST, which is promoter of EMD that enhances the survival of the cancer cell and for most metastases. TWIST expression has shown to be up-regulated in squamous cell carcinoma but has not been investigated in adenocarcinoma.

So after seeking [?] and ethics approval we identified the four groups of patients in this study, 25 patients with Barrett's and no dysplasia, 25 patients with Barrett's and low grade dysplasia, 25 with Barrett's and oesophageal adenocarcinoma, all endoscopic biopsies, and 25 patients where [?] and had evidence of Barrett's, dysplasia and adenocarcinoma, in the section specimens.

The patients were identified randomly through Belfast Link Labs, age was between 60 and 80 years, with a male to female ratio of 3 to 1, and biopsies taken after September '06 were studied to comply with HTA regulations. Paraffin embedded tissues blocks that were archived in the hospital [?]. All cases were fully anonymised, and fresh sections were cut to evaluate the morphology and the diagnosis.

For anybody who has done lab-based research knows how exciting it is, especially for a surgeon. Anyway [?], all slides were scored by two planned assessors and here are the results.

We got lucky really, the first biomarker, P540S, was negative in all the Barrett's tissue, it was over-expressed in low grade dysplasia, over-expressed in adenocarcinoma and the sections. The staining pattern was quite consistent with these investigations. It was observed that racemase was significantly expressed in cases of low grade dysplasia and this could signify its role in the detection of dysplastic progression of Barrett's oesophagus.

The second biomarker, well, gave even more exciting results. It was completely absent in all 25 Barrett's cases, low grade dysplasia, and was positive in six cases of the endoscopic biopsies. That was still statistically significant. And 17 out of 25 cases were positive with CD133. CD133 was demonstrated for the first time ever to be expressed significantly in cases of oesophageal adenocarcinoma. The same characteristics was similar to those seen in cases of colorectal cancer.

The third biomarker was expressed in one case out of 25 for Barrett's oesophagus, three cases of low grade dysplasia, 14 of adenocarcinoma and nine of resections.

However, this staining pattern we achieved with TWIST were different to previously published studies and was the most difficult to quantify. Although primarily nuclear this expression was seen preferentially in the [?]. Nevertheless, TWIST did show increased expression in keeping with our new [?] of Barrett's oesophagus.

In conclusion, all three potential biomarkers investigated in this study demonstrated increased expression in [?] of Barrett's oesophagus and [?] in longitudinal and prospective studies. Thank you very much.

Professor Margaret Cupples:

Thank you very much, any... yes, there's two questions, Stanley?

Dr Stanley Hawkins:

You've done very good, congratulations, good work. The question is did you look at the combination of the three markers, how they all mapped out together?

Dr Jared Ahmad:

No they were not mapped out together, independent sections were cut off each tissue block and they were separated, and independent [?] runs were carried out with different antibodies. So they were done in different batches, one by one.

Dr Stanley Hawkins:

Yes I realise that, but were you able to do a case by case analysis looking at the combinations of different states?

Dr Jared Ahmad:

No we did not do that because we did not have the ethical permission to access patients' case notes.

Professor Brew Atkinson:

I think it's very interesting, and congratulations. I'm a bit puzzled as to how you're going to put it into practice, because you've said that sampling errors are the biggest problem, so can you just tell us how this would help in terms of sampling errors in 25% of cases?—because you might just end up sampling a normal Barratt's oesophagus but decided 25% of cases might have dysplasia or cancerous biomarkers, how would they help you then?

Dr Jared Ahmad:

That's a very interesting question and this is the aim of this project, up to 40% of cases are missed even on surveillance endoscopies, and if we have a biomarker, this was phrase 1 and phrase 2 study, and as you know there are four phases of development of biomarkers, this was the retrospective phase on tissue blocks and now the third stage is prospective screening studies and then longitudinal studies.

So once a biomarker is established, like P540S it is established for prostate adenocarcinoma, we can take a biopsy and also performing immune-staining with the biomarker that is already established and then see if it's expressed or not. If the biomarker for example on Barratt's oesophagus becomes positive, that means this is possibly a covert adenocarcinoma or dysplasia and that person, that patient, needs to be looked for that a bit more closely with a bit more vigorous endoscopy protocol and more biopsies.

Professor Margaret Cupples:

Thank you very much indeed, I think we've... I applaud you for your answers.

And we move quickly towards the area of cardiology, I'd like to invite Magnus Daly to come and take the stage and tell us about his work in looking at echocardiography. Thank you.

Dr Magnus Daly:

Thank you. Thanks to the Ulster Medical Society for inviting me to speak this evening on my work involving heart failure patients at the Royal Victoria Hospital. I'm giving a talk today entitled 'Echocardiographically guided optimisation improves functional response in cardiac resynchronization therapy'.

As we know cardiac resynchronization therapy involves the implantation of biventricular pacing and is an established treatment option for patients with symptomatic congestive cardiac failure. However, up

to 30% of such patients do not respond to electrical resynchronization and this is thought to be due to poor lead placement, sub-maximal pharmacological therapy or myocardial scar tissue. However, cardiac resynchronization therapy optimisation is recommended by the current ESC guidelines and it's not part of routine real work practice at present.

So what is cardiac resynchronization therapy optimisation? It's the process of echocardiographic measurement of changing pacemaker settings in order to maximize the cardiac output potentially. The major cardiac resynchronization therapy studies COMPANION and CARE-HF mandated post implant optimisation, however these used variable protocols and as a consequence of this there's no standard protocol for this echocardiographic optimisation. Bi-ventricular pacing involves atrioventricular and also intraventricular delay. Atrioventricular delay optimisation results in a number of physiological things including increased diastolic filling, increased stroke volume and a reduction in pre-systolic mitral regurgitation.

Sequential left and right ventricle pacing is associated with improvement in ejection fraction and therefore exercise capacity, with also a reduction in pre-systolic mitral regurgitation, and it is these two aspects we wanted to look at in this study.

As we also know, dys-synchrony in patients with congestive cardiac failure manifest as left bundle branch block on their surface 12 lead ECG. Those patients have higher rates of mortality and morbidity. So optimisation of the left ventricular outflow tract velocity time interval, which is a measurement of the peak flow over the left ventricular outflow tract, also known as stroke distance and is a surrogate marker for cardiac output.

This has been shown by a group in Cardiff to result in improvements in both inter- and intraventricular dys-synchrony. A reduction in any dys-synchrony as assessed by echocardiography results in a substantial clinical improvement.

So we hypothesised that using echocardiography, that optimisation of this left ventricular outflow tract velocity, ie stroke distance, and the surrogate for cardiac output, would result in improvements in both the measures of mechanical synchrony assessed by echocardiography and translate into improved functional status.

Between 2008 and 2010, consecutive patients referred for CRT optimisation at the Royal Victoria Hospital were enrolled on inclusion criteria comprised greater than or equal to three months post-device implantation, in New York Heart Association trials three to four and maximum pharmacological therapy, essentially looking for patients who were non-responders to device implantation. We also had sinus rhythm as an inclusion criteria, as of course, as I pointed out earlier, atrioventricular delay is part of the optimisation protocol.

So both pre-optimisation and six month follow up, blood was sampled for NT-proBNP, a cardiac neural hormone which is directly related to cardiac volumetric stretch, six minute walk testing done pre-optimisation over six months, in addition to the quality of life questionnaire, the Minnosota heart failure questionnaire which is a standard.

The optimisation process involved base line parameters of dys-synchrony, septal posterior wall delay, intraventricular delay, which is a calculation based on the difference between aortic and pulmonary pre-ejection time, and also tissue Dopplar opposing wall delay. During the optimisation protocol we changed the intraventricular delay and the atrioventricular delay to obtain an optimal left ventricular outflow tract velocity, and this was then translated into optimal cardiac output. We then recorded all of these parameters again post optimisation to see whether there was any improvement.

Just to go through the optimisation protocol, the top box is the intraventricular delay, we have simultaneous pacing then LV plus 20, 40, 60, 80, and then RV plus 20, 40, 60, 80 milliseconds. We then see what the LVOT VTI is after each of those settings and set the pacemaker to the one obviously that has the maximum velocity.

We then adjust the atrioventricular delay from 80 to 180 milliseconds, set it to the preexisting VB delay and in combination then leave the biventricular pacemaker set at the optimal settings. For continuity and reproducibility, we have a recording done by an experienced echocardiographer in the left lateral position, end expiration, with minimal probe movement.

Overall in the two year period we've had 90 patients referred for CRT optimisation. However, we had to exclude 20 patients due to atrial fibrillation on their attendance, the fact that it was less than three months since their device implantation or that their NYHA class was less than three, so this resulted in an overall cohort of 70 patients. As you can see 81% were male, the mean age was 68 years and 57% had coexisting coronary artery disease felt to be the main aetiological stimulus for their cardiomyopathy. Also, the majority of patients were on maximal dose beta blockade, ACE or ARB medication, and diuretic therapy.

We can see from this graph that pre and post optimisation, the velocity of the LVOT improved from 80 centimeters per second to over 100 centimeters per second, which was a significant improvement in the stroke distance and therefore their cardiac output. When we looked at measures of interventricular dys-synchrony, ie the aortic pre-ejection time, and therefore by extrapolation, the interventricular mechanical dys-synchrony, both improved significantly from pre to post optimisation, the aortic pre-ejection time from 156 down to 113 and the intraventricular mechanical delay from 48 down to 10. Both of these were highly statistically significant.

Looking at intraventricular dys-synchrony, septal to posterior wall delay improved significantly also from 139 down to 18. Intraventricular synchrony within the same ventricle using tissue Doppler, also showed a similar highly significant improvement from pre to post optimisation.

But really probably the most interesting aspect in the clinical application of all of these echocardiographic findings are the functional improvements at six month follow up. All of the improvements in dyssynchrony that we showed acutely have been translated to as highly significant improvement in NYHA functional class between optimisation and pre-optimisation on six months, with the reduction from over 3 to 1.6. The administered Health Heart Failure Public Life questionnaire improved not significantly however, from 41 down to 38. However on sub-analysis this questionnaire consists of both functional and psychological questions and the improvement in the functional aspect of the questions was indeed highly significant, but we couldn't use that as the overall score. Probably most interesting the NT-proBNP improved highly significantly pre-optimisation at the six month follow up implying a significant aspect of reverse remodelling in this patient group, it reduced from over 3,200 to just over 1,200 within in a six month period. Of course patients had some minor adjustments made to their pre-existing medications because they've had improvements in blood pressure and improvements in exercise in capacity, and in fact exercise capacity improved significantly from pre-optimisation to just over 300 meters in six month follow up. So the initial hypothesizes being that the improvements in LVOT velocity would be translated to improvement in stroke volume, cardiac output and therefore increased exercise capacity was obviously proved positive.

One interesting observation just on the back of that is that there was a significant correlation between the improvement in the LVOT velocity, i.e. the stroke distance, and also the improvement in a 6 minute walk distance carried out, so obviously those two are related.

So in conclusion optimisation of the LVOT velocity using sequential adjustment of the biventricular pacing settings can result in significant improvement, not only in the echocardiographic features of dyssynchrony, but also the NYHA symptom-class of patient, their exercise capacity and also their cardiac neural hormones, ie reverse remodeling. This is a correlation between the two and obviously we're continuing this into a longer-term follow up and also additional echocardiographic features. Thank you.

Professor Margaret Cupples:

Thank you very much indeed, one question?

Professor Brew Atkinson:

Do you actually think that everybody who had this done could be having regular resynchronization?

Dr Magnus Daly:

Regular optimisation of their device? Well the recommendations would not be to optimise but there's an auto optimisation that happens when the device is put in but because the lead placement we need to wait for two months afterwards. Yes, everyone should be optimized because the routine would be, in the Royal, that everyone gets simultaneous biventricular pacing and we have shown that actually very few patients respond to that so they need tailored pacemaker settings not a generic setting.

So in answer to your question, yes, everybody would need optimisation at a three months' timeframe. And of course they'll then be re-optimised within six months and a year because of the reverse remodeling then their left ventricle dimensions change and so the position of the leads change and so it needs to be readjusted. So it should be a continuous spectrum of optimisation at six month intervals.

Professor Margaret Cupples:

Thank you. And we're ready to hand over to our next presenter to explain again towards more surgical and pathological aspects of care out of the field of medicine, and I'd like to welcome Phil Davey. Thank you.

Dr Phil Davey:

Good evening ladies and gentlemen, Lady President. I'm going to present a talk on, this was performed in the Ulster Hospital, the clinical use of axillary ultrasound complemented by a fine needle aspiration in the staging of breast cancer.

So breast cancer, it's one of the most common cancers in western society. It affects nearly 46,000 women in the UK. Axillary node status is recognised to fulfill the most significant prognostic factor in patient survival. Clinical examination is notoriously unreliable in detecting lymph-node metastases. Previously surgical clearance for the nodal basin was how these tumours were staged in their axillary levels. More recently in the last 15 year, sentinel lymph node biopsy has revolutionized axillary management of breast cancer. Sentinel node biopsy involves injecting either a radionuclide isotope or blue dye and opening the axilla, and the idea is that the blue dye or the isotope will go to the very first node, the draining node, and that's removed and sent off and that generally then should predict whether the axilla is infiltrated by tumour.

The major drawbacks of the sentinel lymph node are essentially the false negatives; it can be up to 3%. The other problem with sentinel nodes is most of them get reported at at the time of the surgery, and during the operation the histopathologist cuts the node in half, puts it on a slide and does imprint cytology. At a later stage they form the sliced node and look at it again, and so sometimes their initial report at the time of surgery can be inaccurate.

Other problems with sentinel lymph nodes is it increases operating time and as I say, can lead to less cases being done on a list. If the patient knows what's happening beforehand it causes less emotional distress to the patient. Technically the primary surgery is easier to do than having to go back into an axilla that's already been operated on, and if they can know beforehand before surgery there's potential to introduce [neo-adjutant?] chemotherapy and also talk in more detail about reconstructive options.

Ultrasound scanning has come into prominence in breast cancer in the recent years and has been used both to look at the breast lesions and the axilla. In the past three or four years in Ulster it started to be used to look at the axilla and that's where our study comes in.

The aims of our study were really to evaluate the use of the axillary ultrasound complimented by fine needle aspiration and to see how good it was at detecting axillary metastasis prior to patients undergoing any form of surgery. This was their retrospective review and it took place between January and October 2009.

The radiologist classifies the lymph nodes according to their morphological appearance, as well as their size, and they classify them into normal, suspicious and malignant. Of the patients who had a normal ultrasound they would proceed to send a lymph node biopsy. Any patients that were defined as suspicious they underwent a FNA biopsy of the lymph. Those patients that were C1 in suspicion, or C2 benign, would go for a sentinel node biopsy. Any patient that had a biopsy of C3 to C5 would go for a full axillary clearance, any patient whose nodes look malignant on the scan would also go for a full axilla clearance. Any patient who has subsequently had a positive sentinel node would have to come back for a secondary axillary clearance at a later stage.

Looking through… using our theatre log to [find] patients, we found 121 patients. One of these patients had to be excluded as their actual breast specimen did not show any invasive malignancy and one was excluded as their nodes showed chronic lymphocytic leukaemia.

So this is the results of our study and you can see 82 patients had a normal axillary scan, of these 19 ended up having positive pathology and 63 were negative. Those that were suspicious with an FNA of C1 or C2… all our patients who had actually suspicious scan, all of the biopsies were C1 and C2 so we didn't actually identify any of those patients C3 to C5. There were 16 patients, of that two had positive pathology at the end and 14 had negative. Those who were defined as having a malignant scan, 21 patients, 19 had positive pathology and 2 had negative pathology. That shows in our case that ultrasound complimented by FNA has a positive predictive value of 90.4 and a negative predictive value of 78.6, a sensitivity of 47.5 and specificity of 97.5.

What's the impact of this really? Forty patients out of the 119 had positive nodes on their pathology, 21 of these patients had to come back for a second axillary clearance. Two of the patients unfortunately had an axillary clearance that in retrospect was not required, and that was the two patients who had the malignant scan proceeded straight to [?] clearance. So the use of using axillary ultrasound preoperatively resulted in 19 out of the 119 patients avoiding a second axillary procedure. So then we thought let's see what everybody else is doing. So we looked at a number of recent studies from Europe, the USA and from Asia, and you can see our figures at the bottom compared to everyone else. So predicated value is a little bit lower than most peoples, our negative predicative value is about average, and again, sensitivity and specificity appear about average compared to all the other centres.

So what does that mean? Well really at the present time staging an axilla is still best performed by surgical sampling, that's the gold standard. As much as ultrasound and using cytology can identify a number of patients it's not strong enough to have the sensitivity to replace surgical staging. What it does do is it can detect certain patients that are more suitable to go for a full axillary node clearance as opposed to sentinel node biopsy. So we now recommend that every patient who's undergoing either sentinel node or axillary clearance should be assessed using an ultrasound and FNA. And even at centres where you do have intraoperative histopathological reporting it may identify those patients early, that you can just proceed straight to an axillary clearance and prevent having to do a positive sentinel node on them.

What does the future hold? Really, we would hope that as the radiologist experience and scanning develops and their ability to perform an FNA of nodes, the accuracy should also improve. And looking through some studies, some centres are now looking into core biopsy in the lymph nodes, and also looking at different modalities of ultrasound and Doppler to see can they improve their rates. Thank you very much.

Professor Margaret Cupples:

Thank you very much indeed for sticking to time successfully. Can I invite a question?

Audience member:

Sorry, just one quick question, when did you do the ultrasound of the axilla, was that immediately after the ultrasound of the breasts or…

Dr Phil Davey:

Yes, the patients get them both at the One Stop Breast Clinic in the Ulster.

Audience member:

But I mean at the same scan I mean?

Dr Phil Davey:

Yes.

Audience member:

So you would be potentially doing an FNA on the node before you know whether or not the patient has cancer?

Dr Phil Davey:

Yes, if the patient has an ultrasound or mammogram of a lesion, they would probably more than likely get a FNA or a core biopsy of that, at the time, and then you would proceed to scan their axilla, and again, yes, if there was anything suspicious they would have a FNA done of that.

Audience member:

But you wouldn't have the results of the FNA of the breast tissue before doing a FNA of the axilla?

Dr Phil Davey:

No, no not generally.

Audience member:

Were there any cases where the breast biopsy was negative so the patient had a FNA unnecessarily?

Dr Phil Davey:

I don't have the results of that but I think there probably is, yes.

Professor Margaret Cupples:

Do one question more, thank you.

Audience member:

I'm just wondering about the underlying complication rate on FNA with ultrasounds [?]?

Dr Phil Davey:

No, from a retrospective view it's very hard, we just have the clinic letters and pathology reports, it wasn't recorded at any stage that I could see.

Professor Margaret Cupples:

Okay, thank you very much indeed. Now can we invite Claire, Claire Jones to come and tell us a little bit more about radiological investigation and a little bit more in the area of cancer, but in a different area in the body, looking at colorectal and liver metastases. Thank you.

Dr Claire Jones:

Good evening Lady President, ladies and gentleman. Thank you for the opportunity to present a prospective study of imagining modality for colorectal liver metastases.

Colorectal cancer is the second most common cause of cancer-related death in the western world, with over 1,000 cases diagnosed annually in Northern Ireland. Up to 50% of these patients will go on to develop metastases within the first two years of diagnosis of their primary tumour, with the most common metastatic site being that of liver. To detect these metastases the British Society of Gastroenterology guidelines recommends the CT chest, abdomen and pelvis, followed by liver specific imaging as per local protocol. Controversy remains as to which is the most optimal liver imaging modality.

The options include CT arterial portography, or CTAP. This was the imaging modality that was in vogue approximately a decade ago. However, it's still recognised to be sensitive for small tumours, and in fact has not been previously evaluated using current multislice CT scanning. Another option is that of PET CT scanning, this was first introduced in Belfast in 2002 and combines the metabolic information of PET with the anatomical information of CT, and has the added advantage of detecting extra hepatic disease. An MRI is the final option. This has added advantages of improved contrast or spatial resolution with overall better lesion characterization.

So in order to make a decision as to which is the best modality we prospectively compared these three imaging modalities for the detection of colorectal metastases, along with the five year follow up for this group.

To do this, from 2003 to 2004 consecutive patients with colorectal liver metastases, underwent CTAP, MRI and PET CT. Two blinded radiologists for each modality reviewed the scans by consensus. Following the scans the study cohort was broken into two groups. Group 1 were those deemed suitable for surgical resection, at surgery they subsequently went on to have an intraoperative ultrasound, and the radiological findings were subsequently compared to the gold standard of histopathology. For these, sensitivity, specificity, negative and positive predicted value and overall accuracy for each of the investigations was calculated. Group 2 were those deemed unresectable as a result of their scans, and as histopathology was unavailable correlation of results between imaging modalities were determined. Long term survival for both groups was also calculated.

So to begin with some demographics, Group 1 consisted of 19 patients with an even sex distribution and a mean age of 63.4 years. Group 2, those with unresectable disease, a larger group of 36 patients, had a similar age and sex distribution.

So to look at Group 1 first of all, that is those patients who went on to have liver resection. 87 lesions were identified through all three modalities, 40 were reported as metastatic, 25 perfusion defects, five were benign and 17 indeterminate. Histopathology subsequently confirmed 28 liver lesions with three extrahepatic lesions. 15 were identified positively by all three imaging modalities. If we look at this table we can see of the pre-operative staging investigations MRI was the most accurate at 90.6%. CT arterial portography was the most sensitive at 82.1%. You may note the fourth column, this represents intraoperative ultrasound, and it is more accurate, however it's important to note that this was not blinded as the surgeon was aware of the prior imaging results, and also intraoperative ultrasound has more of a role for surgical planning rather than preoperative staging. So to look at the detail, CTAP 25 of the 28 lesions were detected, and three were missed. In the MRI, 22 were detected and six were not seen. And the PET CT only 15 lesions were detected, three were reported as benign and in fact ten were not identified. Of these patients not identified, the common reasons we felt were, they were either post chemotherapy, which the literature would suggest, the PET CT is not as sensitive for patients who have had chemotherapy. And alternatively, in some cases there was a delay of imaging to surgery of up to ten weeks. Interestingly however, three patients had extrahepatic disease detected. This is normally seen as a contraindication to surgical resection, however in fact it was a recurrence at the primary anastomosis site and therefore was

dealt with surgical intervention. The lesions found in all three modalities were smaller than that of histopathology. So with regards to the follow up in this group, 100% were alive of one year, 75% at three years and 43.7% at five years, with the mean overall survival of four years and ten months.

So in Group 2 those with unresectable disease, not surprisingly there was a higher yield of lesions of 213, of which 51 were reported as metastatic by all three imaging modalities. As we do not have the gold standard of histopathology to compare it to we performed correlation between the imaging modalities and found a higher correlation of 62.1% between PET CT and MRI. In this group the most common treatment modality was that of chemotherapy, with Oxaliplatin being the most common first-line agent. Four patients also had radiotherapy, two had radiofrequency ablation, and one went on to have lung resection. If we look at the survival for this group, not surprisingly survival is overall poorer than the operative group. 81.2% at one year, 34.4% at three years and 15.6% at five years.

Therefore Lady President, ladies and gentlemen, to conclude, MRI provides the most accurate liver imaging modality, while PEP CT has the advantage of detecting extrahepatic disease. And finally, we see that this study highlights the favourable five year survival for those patients who are suitable for liver resection. Thank you.

Professor Margaret Cupples:

Thank you very much indeed. Questions for Claire? Our radiologist is going to ask a question for Claire?

Audience member:

It's a quick question about the MRI scanning, was it the same protocol used for all of the patients? Was it a variety of different ways the liver can be looked at?

Dr Claire Jones:

Yes it was standardized as one approach and the same radiologist reviewed each MRI for the patients recruited to that study.

Audience member:

And did you use contrast enhancement for that?

Dr Claire Jones:

No.

Audience member:

No? So there's no use of gadolinium or any of the newer ferrous state?

Dr Claire Jones:

No, not in this, I suppose that's a limitation unfortunately it's a little bit out of date… you know, with having added in the follow up on this group, technology has enhanced since the study so I guess that's a limitation of our findings.

Professor Margaret Cupples:

In the interests of time, I think I'll say, thank you very much indeed Claire.

Thank you very much indeed Scott, can I introduce Scott McCain, who's going to tell us something more about breast cancer, but this time male. Thank you.

Dr Scott McCain:

Lady President, ladies and gentlemen, thank you for giving me the opportunity to talk about male breast cancer treatment outcomes, a retrospective cohort study carried out in the Breast Surgical Unit in the Ulster Hospital, Dundonald.

Male breast cancer is a rare disease with a lifetime risk of 1 out of 1,000 for males. It counts for less than 1% of all breast cancer and 1% of cancers in men. Incidence appears to be on the increase, which is perhaps a reflection of the increasing longevity of the population. Incidents peaks at around age 70 and lacks the normal bimodal age distribution that you would expect with female breast cancer. Risk factors are similar to those of female breast cancer and include increased age, obesity, ionizing radiation, and oestrogen excess, which can either be exogenous for example in men who have been treated for prostate cancer, or endogenous which includes patients with conditions like Klinefelter syndrome, which confers a 30 to 50 times higher risk of developing the disease.

The predominant pathological diagnosis is that of infiltrating ductal carcinoma, which accounts for 90 to 95% of patients, 90% of patients are also oestrogen receptor positive.

Treatment predominately involves surgery initially, mainly in the form of mastectomy followed by axillary node sampling by either sentinel node biopsy or full axillary node clearance. All forms of adjuvant therapy can be considered to include a hormone therapy in the form of tamoxifen, chemotherapy and radiotherapy. However, adjuvant treatment traditionally has a lower uptake in men than in woman. Several studies in the literature have shown that both overall survival and disease-free survival are lower in men than in women. So the objective to this study was to examine patient demographics of all the male breast cancers that were diagnosed, look at the treatment they have received and examine the outcomes that were achieved.

The Ulster Hospital sees approximately 300 patients with breast cancer every year, of these one to two are in men. Unit treatment policy has always been to manage male breast cancer on the basis of pathological staging, tumour biology and co-morbidity, as you would for female breast cancer. Our breast cancer database has been maintained since 1993 and this database was investigated and data taken from the database and confirmed with retrospective chart review. For data which was missing, which included patients whose follow up had been completed, or those who had died, contact was made with their general practitioner for further information. A range of descriptive statistical analysis was employed.

Twenty-four tumours were diagnosed in 22 patients, one patient had metachronous breast cancer and one patient had synchronous breast cancer. The median age of diagnosis was 69 years and the median tumour size was 19 millimeters. Of those tested for hormone receptor status 17 of 17 were oestrogen receptor positive, nine of nine were progesterone receptor positive, and eight of eight were human epidermal growth factor receptor 2 negative. With regards to HER-2 this has only come in vogue over the last five to six years, so this accounts for the low numbers in this group. There was also a period in the 90's where it was thought that tamoxifen would help all patients with breast cancer, even those with hormone receptor negative disease, so it wasn't tested for during this period.

This graph displays a pathological tumour type, with tumour type on the x axis and the number of tumours [?] tumours of each type on the y axis. Infiltrating ductal carcinoma was the predominant type as expected, accounting for 20 out of 24 tumours. This graph displays tumour grade, tumour grade on the x axis and the number of tumours of each grade on the y axis. You can see that the predominant tumour grade was grade 2 and with the remainder being divided equally between grades 1 and 3. This is a similar distribution to other studies that have been published.

These tables display the TNM stage and the overall stage of the cancers that were diagnosed. The predominant T stage was T1 or T2, which accounted for 80% of patients diagnosed. Six patients had node positive disease, with one patient being heavily node positive, one patient had distant metastases at diagnosis. The graph displays the treatment, with treatment on the x axis and the number of tumours on the y axis. Twenty-two patients had mastectomy and two who had gynaecomastia underwent wide local excision. Unfortunately one of these patients proceeded to have a mastectomy due to involvement of surgical [?]. Eleven patients had radiotherapy and all patients were initially commenced on hormone therapy in the form of tamoxifen. One patient experienced a complication when he developed a deep vein thrombosis as a result of his tamoxifen therapy, which was then stopped. Unfortunately this patient proceeded to develop a contralateral breast cancer. No patient had chemotherapy.

We looked at 24 tumours with a medium follow up of 70 months, no patients had local regional recurrence and one patient developed systemic metastases to his lung and to his brain. He's currently alive, 26 months after diagnosis, and is undergoing chemotherapy. The overall five-year survival is 67%; this is comparable with other studies, and felt to be due to the co-morbid population. However, five year disease free survival is 90%; five year disease specific survival is 100%, which is much higher than other studies that have been published. Seven patients have not yet been followed up for a full five years.

So to summarise, this was a retrospective cohort study that's looked at 24 tumours in 22 patients, the medium age at diagnosis was 69 years and treatment principles were employed as you would for female breast cancer and excellent outcomes have been achieved.

So to conclude, Lady President, ladies and gentlemen, male breast cancer is a rare disease; our study has similar demographics in terms of patient characteristics and tumour biology as other studies published. The treatment differences included that we employed radiotherapy and chemotherapy less often but tamoxifen relatively more frequently than other studies have, and we have achieved better outcomes that have been described from the literature for male breast cancer, and similar, and perhaps even slightly better outcomes that have been described for female breast cancer. This was a small retrospective study so we would advise caution in interpreting the results. However, because male breast cancer is such a rare disease, randomised control trials are extremely difficult, so we advise treating male patients with breast cancer the same as you would for female breast cancer, i.e. treat the disease and not the sex. Thank you.

Professor Margaret Cupples:

Thank you, any questions? Okay, can I ask you what you learnt from doing this study? Did it change your practice in any way?

Dr Scott McBain:

Well the thing it confirmed that we were carrying out treatment that achieved great outcomes, certainly in comparison to other studies that have been published. I think we would advise, particularly advocate tamoxifen, especially in hormone or oestrogen receptor positive disease. Perhaps suggest that radiotherapy and chemotherapy aren't particularly important.

Professor Margaret Cupples:

Okay, thank you.

Dr John Craig:

Is there a psychological impact from having the disease that's supposed to only happen to women?

Dr Scott McBain:

Yes, male patients tend to feel excluded, they don't... because they present later... they tend to present at a later stage than females do, so that would tend to influence prognosis.

Professor Margaret Cupples:

Thank you, thank you very much indeed. Can I welcome then Ciara, Ciara McGoldrick is our last presenter this evening, and she's going to expand our knowledge further in this area I think, and this was not any deliberate theme in terms of the presentation for this evening I can reassure you. Thank you.

Dr Ciara McGoldrick:

Thank you Lady President, my name is Caira McGoldrick, I'm a speciality registrar in plastic surgery

based at the Ulster Hospital, and today I would like to present a joint piece of work carried out by ourselves and our oncology colleagues in the Belfast Cancer Centre, on the oncoplastic outcomes on the patients undergoing implant-based breast reconstruction and radiotherapy, and this involves an eight year retrospective analysis.

In terms of background, capsule formation is a recognised complication of implant-based breast reconstruction. A capsule is formed by a normal scar around an implant and incurs in all implant insertion. These become pathological whenever they become high in grade, where they become painful and cause asymmetry.

Knowing that radiotherapy increases the risk of pathological capsule formation, and the published figures are anywhere between 28 and 51%, this patient shows on the right side an evidence of a high grade 4 capsule contraction rate, and you can see that the nipple is displaced and the breast is tethered and it would be quite painful and uncomfortable for that patient.

In terms of the background, we know that implant-based reconstruction has been used for some time and can either be an immediate or delayed procedure. Traditionally this is a two stage procedure where at the initial procedure we inserted a tissue expander, which is expanded over serial visits to clinic, and then when the appropriate size is reached this is then removed at a second operation and replaced with a permanent implant.

In more recent years permanent expander implants have come on the market and this allows a one stage implant-based reconstruction, where the implant has a silicon outer shell and a saline centre. This is how we would do a traditional tissue expander, with the syringe that would be inserting that saline into a port in the axilla, and then the newer implant has silicone on the outside and saline in the inside. So you can see that even when the double lumen implant is deflated there will still be a mound present. It is not known however whether irradiating a permanent implant would cause problems.

If you imagine that the majority of these patients when they are being counselled preoperatively are told that radiotherapy is a contraindication to having an implant inserted, so it's only a very small number of patients with an implant who would go on to receive radiotherapy for that reason.

And this added an extra dimension, if we put an implant in place and then proceeded to irradiate it, how would that affect the patient? Would it interfere with radiotherapy administration? And some papers have been published showing that there is a mathematical probability that radiotherapy would be altered in some way, and this could potentially result in increased rates of local recurrence for our patients.

And indeed from a plastic surgery point of view, would it increase the capsule formation rates? Would these patients go on to have more pathological capsules which will require revision surgery, which from a patient point of view has significant risk.

So for our method we looked at all the patients from the year 2000 to 2009, who'd received... who were under oncology and plastic surgery care, this is a single centre administering the radiotherapy, i.e. the Cancer Centre and the single plastic surgeon in the Ulster Hospital, and the standardized radiotherapy technique which was employed in the year 2000. And we were looking to compare those patients who'd had a one stage implant-based reconstruction from the newer permanent expander implant and those who had a traditional two stage implant-based reconstruction.

Looking at the baseline patient demographics you can see that there were 58 patients who a one stage and 54 patients who a two stage procedure. And the baseline demographics are largely similar, the main age of diagnosis, proportions of cell type, proportions of patients in each stage and grade. Indeed whenever we went on to look at what treatment they'd undergone those treatment patients had received similar proportions of chemotherapy, hormone therapy and Herceptin.

We can see that in terms of radiotherapy, because this is an intention-to-treat principle over a small percentage in each group that did not go on to receive radiotherapy but they were [?] in each group. A small percentage of patients received autologous tissue, that is either the use of a [?] or a latissimus dorsi flap, and the time to follow up was significantly different in that those patients undergoing a two stage procedure takes longer for their treatment to be completed, and they had a slightly longer time to follow up.

This first graph shows the disease recurrence, which whenever you're looking at patients with breast cancer and reconstruction, it has to be their disease recurrence that is the most important, and you can see that the local recurrence rate was equivalent in both patient groups, which is reassuring for us. There was no significant difference in terms of the distance recurrence rate or death, but there are differences amongst those.

In terms of the capsule formation rates you can see the percentage of patients on the y axis, and the groups and the complications that we were looking for along the x axis. So you can see that approximately a third of all patients, whether they received one or two stage reconstruction, developed a capsule. But of those one stage patients, a further third required revision surgery, when almost all of those who underwent a two stage procedure required further revision surgery. This is statistically significant. The rate of implant loss is very low, either due to extrusion or infection.

When we look at when these patients presented with capsules, you can see that those patients with a one stage procedure presented significantly later than those with the two stage procedure. Therefore, in conclusion what this study tells us is that there is no difference in the local recurrence rate between one and two stage implant-based reconstruction, which is reassuring for us as we undertake these reconstruc-

tion options they are not interfering with the patients primary cancer treatment.

In terms of the capsule formation rates, we know that there's no significant difference in capsule formation rates between one and two stage reconstruction, but the two stage group proceeded to revision surgery significantly more frequently. The decision to undergo revision surgery is a very complex one between the patient and the surgeon, and we can't imply any cause to that. The capsules were diagnosed significantly sooner in the two stage group, and again that's difficult to say why, is it that the capsule is more aggressive or the patients have a different psychology at that point in time?

So, our take-home message is the small group of patients with breast cancer who are undergoing implant-based reconstruction and radiotherapy there's the same local recurrence rate. The patients can proceed with their treatment knowing that it's not going to impair the effectiveness of radiotherapy, which is the most important aspect.

In terms of capsule formation we know that this occurs approximately 18 to 24 months following surgery, and so these patients need to be followed up for at least this time. It is possible the outlying patients presented with a capsule formation up to five years following. So these patients really do need to be seen by a plastic surgeon for that length of time. A third of all patients will develop a capsule, those patients undergoing one stage reconstruction with a permanent expander implant a further third will have revision surgery but almost all of our stage two groups will have revision surgery. Thank you.

Professor Margaret Cupples:

Thank you very much Ciara, any questions for the surgical side of the coin?

Professor Phillip Reilly:

I don't think you looked at this in your study, and this is for my own information, is there any difference between recurrence rate for people who have reconstruction surgery, and those who don't?

Dr Ciara McGoldrick:

It's sort of a preselecting group in that those patients that are likely to go on to develop recurrence, ie those with higher stage disease, generally don't opt for reconstruction, so they sort of self-select at that stage. While these patients that we looked at in this are generally self-selecting groups, so these are the patients with lower grade disease and they generally tend to opt for reconstruction. Whether that's true… whether that's right in counselling patients preoperatively is debatable.

Audience member:

I assume all the patients had a partial mastectomy?

Ciara McGoldrick:

No, all of these patients had total mastectomy.

Audience member:

They all had total mastectomy?

Ciara McGoldrick:

Yes. Not necessarily in their first… some of the patients had a wide local excision or partial mastectomy in the first instance but they proceeded to full mastectomy before undergoing their reconstruction.

Professor Margaret Cupples:

Thank you. Any other questions?

Was there any feedback at all from the women themselves in terms of what they thought of the procedure?

Dr Ciara McGoldrick:

For the women it goes from a matter of having one surgery or three operations, and the cumulative effect of sequential surgery on those women, in terms of the complication risk but from a psychological point of view it's also very beneficial for the patients to only have to plan for one operation. And from our point of view as plastic surgeons, dealing with these patients from a reconstruction point of view, to be able to counsel patients with actual hard numbers is very useful.

Professor Margaret Cupples:

Thank you very much indeed. Now, John Craig has been very busy in the background and has got a very efficient computer system, much better than the Eurovision Song Contest could ever hope to do! And I am very happy to announce there's two joint winners of the overall presentations for this evening. Ladies first perhaps I should say, so first of all, Claire Jones, congratulations for being a joint winner, and Jared Ahmad, thank you very much indeed.

And can I remind all of the presenters for posters and oral presentations that there is a certificate to justify your hard work, and for the two winners we will be posting out to you something extra in commendation.

Can I thank everyone for coming this evening and supporting the young members of our profession, who I think can assure us that the quality of our professional care will be continuing well into the future.

And just finally to invite you all to our next meeting on the 18th of November in the Health Sciences building, and if anyone wants to know where that is I do have a map this evening to show you! And the subject that night will be The Scarlet Thread and it will be presented by the coroner Mr John Lecky, and he tells me he's not going to use PowerPoint so I'm not quite sure what he's going to bring with him but I look forward to hearing him and I hope you will come too.