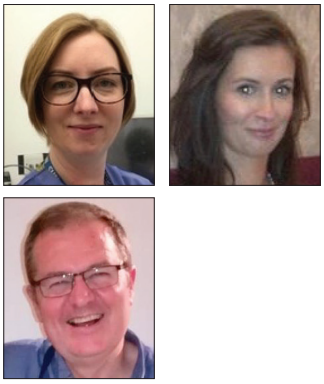
Prospective surveillance with bioelectrical impedance to guide early treatment of breast cancer-related lymphoedema



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Introduction: Early detection and treatment of upper-limb lymphoedema following axillary surgery for breast cancer can reduce symptomatic disease. Bioimpedance spectroscopy (BIS) can be used to identify increased extracellular fluid volume. **Aim:** The aim of this study was to determine the rates of lymphoedema identified by prospective surveillance with BIS and the effects of early identification on patient outcomes. **Methods:** Patients undergoing axillary surgery for breast cancer had BIS measurements recorded pre-operatively and quarterly for 1 year to assess any changes or development of clinical signs of lymphoedema. A reading indicating an increase in extracellular fluid volume led to treatment with a compression sleeve, skincare management and exercise as per departmental protocol. **Results:** 354 patients were included in the final analysis and mean follow up was 50 months. Of these, 10.7% (*n*=38) of patients had an abnormal BIS reading indicating early lymphoedema, while a subset of 6.5% (*n*=23) of patients required referral to specialist lymphoedema services. Of patients who underwent early treatment, 58.8% (*n*=20) did not require any further long-term management. **Conclusions:** Abnormal (ratio values above the normal range, or values that have changed by at least 10 units from the baseline) BIS is a significant predictor for developing lymphoedema. This can be utilised in a prospective surveillance model, to direct early therapy and potentially reduce the incidence of clinically significant lymphoedema, however, further randomised controlled studies would be required to confirm this.

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Recent changes in the management of breast cancer have led to a less invasive surgical approach (sentinel node biopsy, SNB) for the assessment of spread of disease (Krag et al, 2010; Giuliano et al, 2011). It is generally accepted that SNB results in a lower incidence of lymphoedema compared to axillary lymph node dissection (ALND) (Mansel et al, 2006). Reported lymphoedema incidence rates vary widely (13–65%), largely due to inconsistencies in methods of detection and diagnostic criteria (Paskett et al, 2012).

Lymphoedema describes the accumulation of water, plasma proteins, extravascular blood cells, and parenchymal/stromal elements, within the extracellular space (International Society of Lymphology, 2013). The most common cause is secondary lymphoedema, most often consequent to axillary surgery. Lymphoedema is a chronic, 'incurable' condition often leading to a reduction in quality of life (Morgan et al, 2005). Appropriate management involves early identification, therapy to reduce swelling and institution of lifelong maintenance therapy (Devoogdt et al, 2010).

The incidence of clinically evident lymphoedema can be reduced by early treatment (Boccardo et al, 2009; Torres Lacomba et al, 2010). Early detection to guide early treatment can potentially be facilitated by bioimpedance spectroscopy (BIS), which is a reliable,

Table 1. Lymphoedema rates per procedure, as defined by abnormal BIS and need for referral to lymphoedema services.

Surgical Procedure	Number of patients	Patients with abnormal BIS readings (%)	Patients requiring referral to lymphoedema services (%)
All	354	38 (10.7)	23 (6.5)
SLNB	220	10 (4.5)	5 (2.3)
ALND	108	22 (20.4)	14 (13)
SLNB and ALND	26	6 (23)	4 (15.4)

Table 2. Numbers of patients requiring referral to lymphoedema services according to BIS results. (*P*<0.0001).

	Not referred to lym-phoedema services	Referred to lym-phoedema ser-vices	Total
Normal BIS	311	5	316
Abnormal BIS	20	18	38

reproducible, non-invasive method of detecting extracellular fluid space changes at a pre-clinical stage (Ward, 2009). Prospective surveillance with BIS for patients undergoing breast cancer surgery has been standard practice in this unit since 2008. The aim of this study was to determine the rates of lymphoedema identified by prospective surveillance with BIS and the effects of early identification on patient outcomes.

Methods

A retrospective review of all patients undergoing axillary surgery for breast cancer over a 6-year period in whom BIS had been measured as per unit protocol was performed. Data were obtained from contemporaneous patient notes, physiotherapy records and electronic care records. BIS was measured preoperatively using a handheld L-Dex U400 device (ImpediMed) at the patient's bedside. This was repeated in the physiotherapy department at quarterly intervals up to 12 months postoperatively compared with baseline.

If a reading indicating an increase in extracellular fluid was obtained, a presumptive diagnosis of lymphoedema was made and treatment instituted, irrespective of clinical findings. Treatment consisted of a measured compression sleeve garment, and both verbal and written advice on exercise with sleeve on and skincare regimens. Patients were subsequently reviewed monthly. Clinical signs or failure of readings to return to normal initiated referral to specialist lymphoedema services, at which point BIS follow-up ceased. Relevant comparisons were made using a Chi-squared test (Microsoft Excel 2010), with a *P* value of <0.05 considered significant.

All patients undergoing a unilateral axillary procedure for breast cancer between 2008 and 2014 were eligible. For subsequent inclusion in analysis, pre-operative measurements were required in addition to at least two postoperative readings. Patients who had bilateral procedures, previous axillary surgery, a pacemaker, a history of upper-limb DVT, arteriovenous fistulae, or upper-limb fracture and those who were pregnant were excluded, as the use of bioelectrical impedance was precluded.

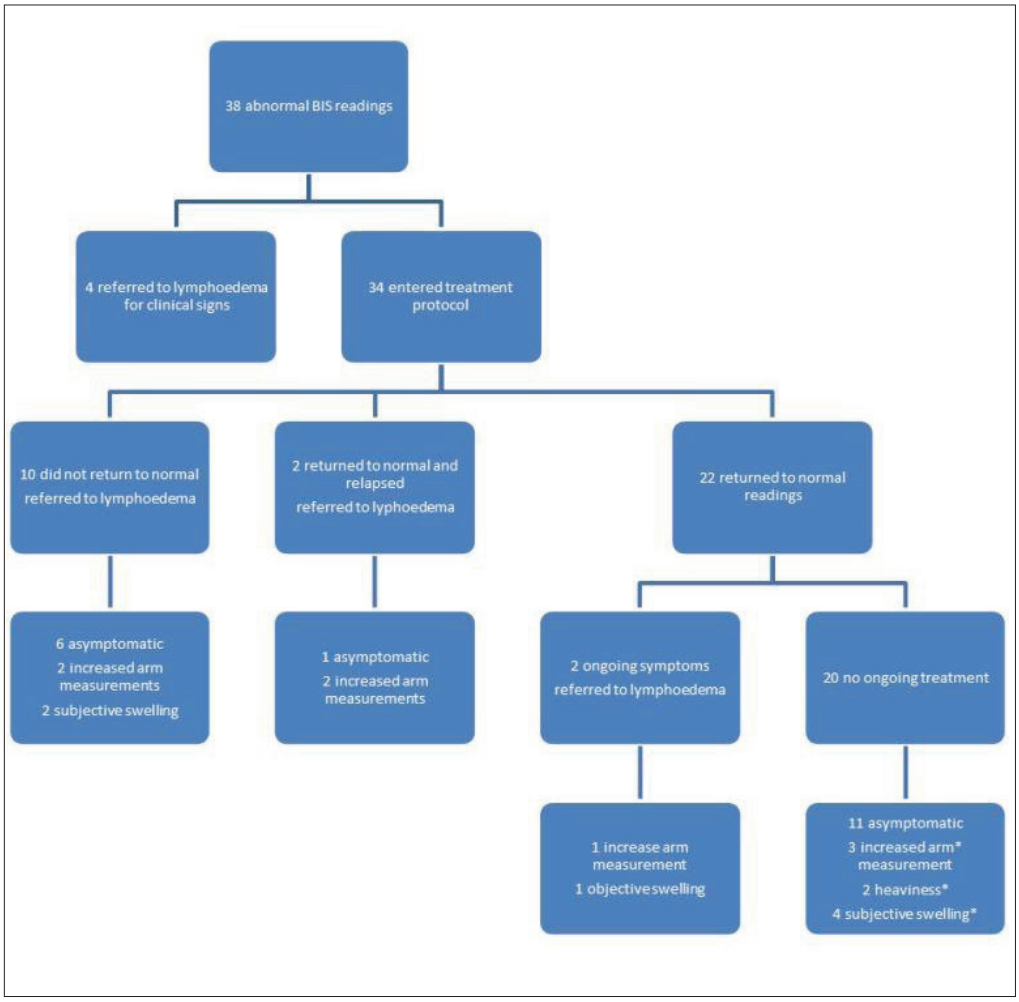
Results

Referral to the physiotherapy department was made for 612 patients. A total of 258 were excluded from further analysis, for the following reasons: 73 had no pre-operative reading recorded, 169 did not attend at least two follow-up appointments (26.7% attrition rate), six had previous surgery, five underwent bilateral procedures, two patients had upper limb DVTs, one had an arteriovenous fistula, one had a pacemaker and one was pregnant.

The final analysis included 354 patients. All patients were female, mean age 59.6 (29–89 years). A total of 220 patients had a sentinel lymph node biopsy (SLNB), 108 had axillary lymph node dissection (ALND), and 26 patients had a SLNB with a subsequent ALND. Mean length of follow-up was 50 months (range of 12–80 months).

Overall, 10.6% of patients (*n*=38) had early lymphoedema, as defined by an abnormal BIS (L-Dex ratio values above the normal range, or values that have changed by at least 10 L-Dex units from the baseline) reading *[Table 1]*. As expected the rates differed according to procedure (4.5% SLNB, 20.4% ALND, 23% SLNB with subsequent ALND). A total of 6.5% of patients (*n*=23) ultimately required referral to lymphoedema services. Again, this differed according to procedure (2.3% SLNB, 13% ALND, 15.4% SLNB with ALND). Significantly, more

Figure 1. Patients with abnormal BIS readings.



patients with an abnormal BIS required referral to lymphoedema services than patients whose readings did not differ significantly from baseline (18/38 versus 5/313; *P*=<0.0001) *[Table 2]*. Of the patients requiring referral to lymphoedema services, 75% of patients (*n*=18) were initially identified by an abnormal BIS reading.

No significant change in BIS readings from baseline occurred in 89.5% of patients (*n*=316). Of these patients, five (1.6%) with no abnormal BIS readings were referred as they were complaining of subjective symptoms (arm heaviness, swelling) without any clinical signs or increase in arm measurements. One patient presented having had normal BIS readings throughout the routine follow-up, with symptoms and a corresponding abnormal BIS reading, giving a negative predictive value of BIS, over a 12-month period of 99.67% (95% CI: 98.19 %–99.95 %). This patient was treated according to protocol leading to resolution of symptoms and return of BIS to baseline. Specialist lymphoedema referral was not required.

An abnormal BIS reading was recorded in 38 (10.7%) of the patients, four had concurrent clinical signs, indicative of lymphoedema and were referred directly to specialist lymphoedema services. Subjective symptoms were present in nine of the patients. A slight increase in arm measurements was recorded in eight of the patients. However, 17 patients were asymptomatic and had no change in arm measurements.

Of the patients with an abnormal BIS reading, 34 received treatment as per protocol *[Figure 1]*. Long-term treatment for lymphoedema was not required in 20 (58.8%) of these patients, as they were asymptomatic and BIS readings returned to baseline. Referral to the specialist lymphoedema services was required for 14 patients (41.2%). In two of these cases, BIS readings returned to baseline, but patients continued to complain of subjective symptoms; in 10 cases, BIS readings did not return to baseline despite treatment and in two cases an initial return to baseline subsequently relapsed.

Discussion

Bioimpedance spectroscopy

Bioimpedance spectroscopy utilises the concept that the magnitude of the opposition to flow

of an electric current is inversely proportional to the volume of fluid in the tissue (Rockson, 2010). Using this method, an early increase in extracellular fluid, rather than simply an increase in volume (the basis of most other detection methods), can be identified. Thus, BIS should allow for early pre-clinical detection of potential lymphoedema and facilitate early intervention. Measurement involves placement of four electrodes in standard positions, and the rapid passage of a small painless electrical current between them (Ridner et al, 2009). Measurements are reported as a Lymphoedema Index score (LDex), which has been validated for clinical use (Ward et al, 2011). Using the L-Dex U400 device (ImpediMed), an abnormal reading is based on a change of more than 10 LDex units from baseline. BIS is reproducible and amenable to bedside or outpatient use, with relatively inexpensive equipment (Ward, 2009; Ridner et al, 2009).

Previous studies have primarily looked at the accuracy of BIS in patients with known lymphoedema, and whether BIS can pre-empt clinical signs, but study numbers are small. Positive correlation with increased arm circumference measurements in patients with clinical lymphoedema has been reported in a cohort of 15 patients (Ward et al, 1992). In a comparison of patients with known lymphoedema and healthy controls, BIS was able to distinguish between the two groups with a greater degree of accuracy than measurements of arm volume (Cornish et al, 1996).

In 2001, a cohort of 102 patients undergoing surgery for breast cancer was followed up prospectively without instigation of treatment. BIS readings for the 20 patients who developed clinical lymphoedema had been abnormal up to 10 months prior to clinically evident swelling (Cornish et al, 2001). Although these studies were limited, a reasonable conclusion is that BIS is able to identify lymphoedema at a preclinical stage with a high level of sensitivity and specificity (Ward, 2009; Rockson, 2010).

In this study, the majority of patients did not develop lymphoedema, either clinically (symptoms or signs) or as defined by BIS. To date only one patient has developed subjective signs associated with abnormal BIS following completion of follow-up at 14 months. This patient received successful early intervention and has not required long-term treatment. This is in keeping with previous reports of high levels of sensitivity. The mean duration of follow-up in this study is in excess of 48 months; although these findings are encouraging, it is recognised that lymphoedema can develop many years following surgery for breast cancer.

Initial lymphoedema rates as defined by BIS readings are similar to previous reports of clinical lymphoedema, with an expected difference according to measurement procedure (Mansel et al, 2006). A similar pattern according to procedure was seen for those requiring referral to lymphoedema services; however, the overall proportion was lower following intervention (10.6% abnormal BIS versus 5.9% referred to lymphoedema services). Over 50% of patients considered to have early lymphoedema as defined by an abnormal BIS reading, did not require any long term management following initial intervention. A direct correlation cannot be made in this observational study, given the lack of control group; however, taken in context with the aforementioned study by Cornish et al (2001) where all patients with abnormal BIS went on to develop clinical lymphoedema, it is suggested that early intervention (guided by BIS) may prevent the development or reduce the severity of clinical lymphoedema, thus improving patient disability and treatment costs.

Prospective surveillance

Traditional models to identify breast cancer-related lymphoedema have relied on a combination of patients self-reporting symptoms, clinical examination, and arm circumference measurements (Paskett et al, 2012). Inherently, this means many patients are not identified until lymphoedema is clinically apparent, rather than at a preclinical stage. The aims of subsequent treatment are to reduce swelling, restore physical function, and improve cosmesis of the affected limb. This can range from monitoring with compression garments to complex decongestive therapy and, in some circumstances, surgical intervention, depending on clinical severity (Koul et al, 2007).

Such lymphoedema significantly impairs quality of life among breast cancer survivors, along with a financial burden to healthcare providers (Morgan et al, 2005; Shih et al, 2009) It is not surprising that studies using predictive models to estimate costs have shown a potential benefit in using prospective surveillance, which can offset the cost of BIS (Bilir et al, 2012; Stout et al, 2012).

It is widely accepted that, for patients with lymphoedema, early instigation of treatment is associated with better outcomes (Boccardo et al, 2009; Torres et al, 2010). Prospective surveillance to enable early identification and facilitate this early intervention is therefore potentially advantageous (Gergich et al, 2008). Currently, BIS

is not widely utilised and, as such, no protocol for its use is available; however, it is recognised as a suitable alternative or adjunct to diagnosis within the National Lymphoedema Network guidelines (2011). These guidelines recommend baseline pre-operative arm measurements for all patients undergoing surgery for breast cancer with repeated clinical assessment and measurement as required at review appointments.

There are inherent difficulties with this approach. Increasingly, breast cancer patients undergo day-case surgery and along with rationalisation of routine clinical follow-up, opportunities to monitor and identify patients developing lymphoedema are reducing. Within this Unit's protocol, patients attending day-of-surgery were identified to the physiotherapy department in advance, enabling preoperative baseline measurements. Subsequent surveillance was carried out independently of breast cancer follow-up. Exclusion of 74 patients due to lack of baseline measurements, along with a high attrition rate for review appointments, demonstrates some of the logistical issues in follow-up with these patients.

Conclusion

Abnormal BIS is a significant predictor for development of subsequent lymphoedema. This study describes a prospective surveillance model, which can be utilised in clinical practice to direct aggressive early therapy. There is potential to reduce the incidence of clinically significant lymphoedema, however, further randomised controlled studies would be required to confirm this. WINT

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