NICE Medical Tech Assessment

WS2 BEA study to determine the optimal method of detection and threshold for lymphoedema intervention: A multi-center prospective study

Background

- A complication of axillary node clearance (ANC) for breast cancer is that patients have an increased risk of developing arm lymphoedema.
- Early detection of arm swelling is recommended by comparing pre-surgical arm measurements with repeated measurements after surgery.
- Early detection may enable early intervention which may prevent the development of lymphoedema
- This prospective multi-centre study evaluated arm volume measurements in lymphoedema in 1100 women to define an optimal threshold for intervention to prevent lymphoedema.

Methods

- Out of the 1100 women recruited to the trial, 629 women undergoing axillary node clearance (ANC) surgery for breast cancer from 9 centres in England, median age is 55 years (range 22-90 years), have undergone pre-operative and subsequent regular measurements post-surgery (1, 3, 6, 9, 12 months, then 6 monthly), of arm volume by perometry (Perometer 350 NT; www.pero-system.de) and multi-frequency bioimpedance spectroscopy (BIS) (L-Dex® U400; www.impedimed.com) measurements and currently have minimum 24 months follow-up surveillance,.
- Change in arm volume was calculated using relative arm volume change (RAVC).
- The primary endpoint of lymphoedema was defined as ≥10% limb volume change compared to the contralateral arm by perometry [1].
- BIS L-Dex change of 10 was considered diagnostic of lymphoedema.

The optimal threshold for intervention in lymphoedema and predictive risk factors for the development of lymphoedema were assessed using Cox regression, log -rank and Kaplan-Meier analyses.

Methods

There is considerable variation in the definitions of lymphoedema and methods of measurement, ranging from the more conservative ≥10% limb volume change (LVC) by perometry, through changes of 200 mls by perometry, to the more liberal increase of 2cm in circumference [2]. For the purposes of this study, we used a greater than 10% arm volume increase (AVI) since baseline (compared to the contralateral arm) as measured by perometer on at least two occasions to identify women with lymphoedema secondary to axillary node clearance [3]. Lymphoedema determined by BIS is a difference of ≥10 units from baseline.

Arms were measured using a 350S perometer with standard perometer software supplied by Pero System, Germany. The average of 2 perometer measurements was used at each visit to exclude intra-observer variability.

Intracellular fluid was measured using the L-DEX®U400 bioimpedance spectroscopy device on loan from ImpediMed Ltd., Australia.

At least 50% of breast cancer patients gain weight in the first year after diagnosis, and this is often associated with increased risk of lymphoedema. Nonetheless, if careful contralateral arm measurements are not performed, weight gain, rather than true lymphoedema, can lead to inappropriate fitting of compression sleeves. BIS results are unaltered by weight gain and we tested whether the BIS results were similar to, more sensitive and/or more specific than, perometer measurements in detecting early arm swelling.

Self-reported symptoms

Patients were asked to complete a lymphoedema questionnaire which used 3 items from the Lymphedema and Breast Cancer Questionnaire (LBCQ) about heaviness, numbness and swelling, as well as FACT-B+4 Health Survey Questionnaire and the EQ-5D in order to assess self-reported upper limb symptoms, physical functioning and quality of life respectively. All questionnaires were completed pre-operatively and then again at 3 and 6 months post-surgery, with the exception of the EQ-5D which was not completed at 3 months post-surgery.

Statistical analysis

Statistical analysis included sensitivity and specificity analysis of the BIS L-Dex score against the 'gold standard' perometer assessment at 6 and 18 months using statistical techniques recommended by Bland and Altman [4, 5]. The BIS value cut off level was checked using ROC analysis and confirmed using later results. Assessment of the relationship between the two methods of measurement up to 2 years in predicting lymphoedema was performed.

The analysis for the current report involved comparison of the baseline and 6 and 18 month post-surgery measurements using paired t-tests and data were described using means and ranges, sensitivity and specificity, univariate and multivariate analyses. ROC analysis and Cox regression and Log-Rank testing was performed for univariate and multivariate analyses. Descriptive methods were used for all other data presented.

Results

Out of the 1100 patients entered into the study, we report data from the first 629 (all with a minimum 24 month follow-up), their median age is 56 years ranging from 22 to 90, 42% had a mastectomy and ANC, 89% were node positive., 66% had a histology of infiltrating ductal carcinoma and the majority (82%) were ER positive(table). Seventy-eight percent received post-operative radiotherapy, 65% received chemotherapy and 81% were given endocrine treatment.

Forty-one patients (7%) had no post 1 month perometer measurements. A further 117 (19%) were lost to follow-up by 24 months. Median time to developing lymphoedema was 12.0 months (range: 2.5-60.8).

Lymphoedema incidence (RAVC of $\geq$10%) is shown below (*Table 79*). The cut-off of 10% showed the strongest relationship with quality of life measures at 18 and 24 months compared to other cut-off values.

Using time to diagnosis of lymphoedema and Kaplan-Meier estimates of those developing lymphoedema by each time point, 15.6% were diagnosed by 12 months and 24% of women by perometry and in 45% of women by BIS by 24 months.

References

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