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Tumour grade on core biopsy and evidence of axillary involvement on ultrasound predicts response in elderly co-morbid patients treated with primary hormone therapy for oestrogen receptor positive breast carcinoma

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ABSTRACT

Introduction: Treatment of women with oestrogen-receptor positive breast cancer who are high risk for general anaesthetic remains controversial. Current guidance is based on studies pre-dating aromatase inhibitors (AIs) which may have also included hormone-receptor negative patients. Such studies have demonstrated improved disease-free survival and local disease control following surgery when compared with primary hormone therapy (PHT) alone. However uncertainty persists regarding benefit of surgery over optimal hormone treatment in patients with significant co-morbidity.

Method: Retrospective cohort study comparing efficacy of PHT in oestrogen-receptor positive breast cancer patients considered unsuitable for surgery. Co-morbidity was scored retrospectively using the Charlson Index. Overall survival and disease specific survival were noted and multivariate analysis performed to identify predictors of treatment failure.

Results: 106 patients treated for breast cancer at Southampton University Hospital with PHT without surgery were identified (Mean age 84.1 years, range 48–101). 94.3% had a probability of 10 year survival of 2.25% or less according to the age-weighted Charlson score. Kaplan–Meier analysis demonstrated a four-year survival of 30% and breast cancer specific survival of 60%. Cox proportional hazards model demonstrated high-grade disease (grade III vs. grade I/II: HR = 2.007; 95% Confidence Interval (CI) = 1.004–4.014. $P = 0.049$) and ultrasound axillary staging (indeterminate/definite lymphatic involvement vs. no involvement: HR = 1.944; 95% CI = 1.010–3.742. $P = 0.047$) independently predicted early failure of PHT.

Conclusion: A high proportion of elderly and comorbid patients die with breast cancer rather than from breast cancer. Elderly comorbid patients who initially respond to primary

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hormone therapy have a less than 30% incidence of delayed treatment failure during their life time; however patients with grade III disease or an abnormal axillary ultrasound are twice as likely to fail first choice PHT.

Introduction

The Second All Breast Cancer Report, which details contemporary practice within the UK, documented that the proportion of patients diagnosed with breast cancer and treated without surgery increases with age[1]; 90% of women under the age of 50 receive some form of surgical treatment compared with 39% of women aged 80 or above and 15% of those over 90. A recent survey of practice within the UK demonstrated 93% of breast surgeons who responded use primary hormone therapy in elderly unfit patients.[2] This is despite current National Institute of Health and Clinical Excellence (NICE) guidance advocating surgery with adjuvant systemic therapy for non-metastatic breast cancer across all ages unless co-morbidities preclude surgery.[3]

NICE guidelines are based on the results of a meta-analysis of trials comparing surgical excision with endocrine therapy verses endocrine therapy alone[3] performed by Hind et al.[4] Analysis was performed on a total of 1076 women enrolled in 3 separate trials of surgery with adjuvant tamoxifen therapy versus tamoxifen therapy alone[5–7]; pooled outcome data suggested a trend toward improved overall survival in women receiving surgery which narrowly failed to reach statistical significance. The disease-specific survival, disease-free survival and local recurrence rates were all significantly improved with surgery.[4] Interpretation of these findings should, however, take into account several shortfalls in the design of the included studies; firstly, only one of the studies[7] excluded hormone receptor negative patients, which could reasonably be expected to bias comparison against primary hormone treatment. Secondly all three studies utilised tamoxifen, therefore no data is available comparing efficacy of aromatase inhibitors (AIs) versus surgery with optimum adjuvant endocrine treatment. Thirdly, all three studies included patients who were otherwise considered fit for surgery and so it is difficult to draw conclusions from these studies about patients considered unsuitable for surgery. Finally the co-morbidity of the patients was not systematically evaluated.

Long-term control of disease with endocrine therapies alone results in local progression or metastatic disease in 45–82% of patients.[6,8–10] Short term data is available from observational studies from the Netherlands and trials of neo-adjuvant endocrine therapy. Wink et al. described 184 unselected patients managed with endocrine therapy alone; 65% of patients avoided progression after mean follow-up of 31 months[11] despite 16.3% of patients having unknown hormone status and 4.9% being oestrogen receptor negative. In the neo-adjuvant setting, letrozole induced tumour stasis or regression in 88% of oestrogen-receptor positive patients following 16–24 weeks of treatment.[12] Meta-analysis of AIs versus tamoxifen suggests AIs are superior in the neo-adjuvant setting, demonstrating a higher response rate than tamoxifen.[13,14] Therefore primary hormone treatment, in the presence of significant co-morbidity which is likely to limit life expectancy, may be a potential strategy for short-term control of tumour progression, limiting breast-cancer specific morbidity and mortality whilst avoiding invasive surgical management.

University Hospital Southampton Breast Surgical Unit reserves primary hormone treatment (PHT) for patients considered unsuitable for surgery due to co-morbidity. The aim of this study was to identify predictive factors which allowed the identification of patients at high risk of disease progression on primary hormone therapy.

Methods

Patient selection and data collation

The study population was identified from a prospectively collated database recording histology and treatment plans for all breast cancer patients discussed within breast cancer MDT meetings at University Hospital Southampton NHS Foundation Trust. All patients diagnosed between June 2006 and March 2010 with oestrogen-receptor positive breast cancer whose initial management was hormone therapy in isolation were identified. Patients undergoing primary surgery, radiotherapy or chemotherapy did not meet the inclusion criteria for this study of treatment failure following primary hormone therapy.

Patient data was collated retrospectively from clinic case-notes and electronic records of histopathological and radiological test results. Patients eligible for inclusion must have had a diagnosis of oestrogen-receptor positive invasive carcinoma of the breast confirmed by core biopsy. Patients with carcinoma-in-situ only, oestrogen-receptor negative disease or lack of histological confirmation of diagnosis were excluded.

Patient management

Patients were diagnosed according to standard unit protocol utilising a combination of clinical review, mammograms, ultrasound examination and histological assessment of core biopsies. Axillary staging was performed by ultrasonic evaluation and fine needle aspiration or core biopsy of suspicious nodes. In the absence of symptoms of metastatic disease neither cross-sectional imaging nor radionuclide bone assessment were performed. Patients were identified as appropriate for primary hormone treatment following Multi-Disciplinary Team (MDT) discussion and consensus agreement regarding the patients' unsuitability for surgery and oestrogen receptor status. Suitability for surgery was