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Title: **What influences healthcare professionals' treatment preferences for older women with operable breast cancer? An application of the discrete choice experiment.**

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Abstract:

**Introduction:** Primary endocrine therapy (PET) is used variably in the UK as an alternative to surgery for older women with operable breast cancer. Guidelines state that only patients with "significant comorbidity" or "reduced life expectancy" should be treated this way and age should not be a factor.

**Methods**: A Discrete Choice Experiment (DCE) was used to determine the impact of key variables (patient age, comorbidity, cognition, functional status, cancer stage, cancer biology) on healthcare professionals' (HCP) treatment preferences for operable breast cancer among older women. Multinomial logistic regression was used to identify associations.

**Results**: 40% (258/641) of questionnaires were returned. Five variables (age, co-morbidity, cognition, functional status and cancer size) independently demonstrated a significant association with treatment preference ($p<0.05$). Functional status was omitted from the multivariable model due to collinearity, with all other variables correlating with a preference for operative treatment over no preference ($p<0.05$). Only co-morbidity, cognition and cancer size correlated with a preference for PET over no preference ($p<0.05$).

**Conclusion**: The majority of respondents selected treatment in accordance with current guidelines, however in some scenarios, opinion was divided, and age did appear to be an independent factor that HCPs considered when making a treatment decision in this population.

Key words: Breast cancer, primary endocrine therapy, surgery, discrete choice experiment, older.

Introduction.

A third of new breast cancer diagnoses occur in women age over 70 years in the UK [1]. This proportion will continue to increase as the population ages [2]. Older patients have higher rates of comorbidity and frailty so that the risk of death from breast cancer is relatively reduced, with only 23% deaths due to breast cancer for patients diagnosed in their mid-80s compared to 73% for patients diagnosed in their 50s [3]. Older patients with operable breast cancer may be offered alternative treatment modalities, such as primary endocrine therapy (PET) [4, 5], wherein oestrogen receptor (ER) positive disease may be treated with endocrine therapy alone.

A Cochrane review comparing PET with surgery based on trials conducted over 20 years ago demonstrated no difference in overall survival between the two treatments, however there were superior rates of local disease control in the surgical group [6]. None of these studies assessed the impact of comorbidity or frailty, and a recent review of case series indicated that older frailer women tend to be treated with PET and have inferior overall survival rates as would be expected due to higher other-cause mortality [7].

National audits have demonstrated significant variation in the use of PET to treat older women across the UK [8] which is not fully explained by case mix variation (stage, deprivation, etc.) [9]. Healthcare professional (HCP) preference may be a source of some of this variation [10] and this factor may exert a potent influence on patient choice [11]. A recent study demonstrated considerable variation in HCP opinion regarding the factors important in breast cancer treatment decision making in this population [12].

This aim of this study was to use Discrete Choice Experiment (DCE) methodology to determine the impact of key variables on HCP treatment preferences for the management of operable breast cancer in older women. DCE is a rigorous survey methodology capable of eliciting individuals' preferences in controlled experimental conditions, through responses to hypothetical scenarios [13], based on the assumption that the patients in the scenarios can be described by certain characteristics and that an individual's treatment preference depends upon these characteristics [14].

Materials and Methods:

The DCE method was chosen to establish HCP preferences in controlled experimental conditions using hypothetical scenarios. Key variables were identified and selected using the relevant literature and subdivided into levels of clinical severity based on clinical expert peer review. Table 1 shows the variables and levels. Twenty-five scenarios were randomly generated using IBM SPSS version 21 Orthoplan software out of 3,072 potential scenarios. For each scenario the participants were asked to indicate a preference for PET or operative treatment for a hypothetical older woman with operable breast cancer. In order to optimise reality in clinical practice, an "opt out" option was included, whereby respondents could indicate no preference for either treatment choice [15]. It was felt that this would more closely reflect HCP decision-making and therefore enhance response rates compared to the more conventional pair-wise choice design [16].

We calculated that in order to estimate the preference for a given scenario with a reasonable degree of precision of say +/-6% (assuming a 50% preference) i.e. 95% confidence interval 44% to 56% would require 250 responders to the survey.

To be effective, scenarios must be plausible and so the questionnaire was piloted with a selection of experienced HCPs who identified eight of the 25 scenarios as being unrealistic. These were excluded from the final instrument. An experienced geriatrician, together with a panel of clinical breast specialists, examined the plausible scenarios and estimated the predicted life-expectancy for each hypothetical patient based on their age, levels of co-morbidity, cognition and functional status, which were categorised as <2 years, 2-5 years and >5 years. Life expectancy of less than 2 years would be an indicator that primary endocrine therapy would be a good choice with minimal morbidity in a woman in whom the breast cancer is unlikely to contribute to the cause of death. Conversely as literature suggests that the median duration of disease control with PET is 2 years, use of this treatment option for a woman with an estimated life expectancy of more than 5 years would be unlikely to result in long term disease control without change of management. The predicted life expectancy of each patient scenario was NOT shown to the questionnaire respondents as this information would not be routinely available in normal clinical practice. Figure 1 illustrates a scenario example. The final 17 discrete choice scenarios were incorporated into a postal questionnaire that was mailed to all clinician and nurse members of the UK Association of Breast Surgery (ABS). An electronic reminder was sent via email to all members after four months. University of Sheffield Research Ethics Committee approvals were obtained (SMBRER243).

Since the outcome for each scenario had three nominal levels ("for operation", "for PET", "prefer both equally") multinomial logistic regression was used to identify associations between the

outcome variable (treatment preference) and the various clinical characteristics given in the scenarios (patient age, comorbidity, cognition, functional status, cancer stage, cancer biology). A multinomial logistic model was fitted in Stata (Statacorp version 13) with “prefers either” as the reference category. Robust standard errors for the regression coefficient estimates were used to calculate confidence intervals and P-values to allow for the clustered nature of the data since outcomes were clustered by participant to take into account the lack of response independence (as each participant answered 17 scenarios).

Results:

Questionnaires were sent out in February 2014. Of the 641 questionnaires distributed, 258 were returned (40.2% response rate): 45.6% male, 53.2% female, 75.4% breast surgeons, 21.8% clinical nurse specialist, 2.0% others (oncologists, breast physician, plastic surgeons). The median age of respondents was 50 years (range 28-69 years). Of these, 4 did not complete the DCE section as they were oncologists or plastic surgeons.

The 258 responders answered 4,281 of the 4,386 scenarios (258 x 17). In 53% (2,279/4,281) of the scenarios, responders preferred operative treatment, 25% (1063/4281) PET, and 22% (939/4281) preferred both equally. Seventy-eight percent (199/254) of responders demonstrated a preference for operative treatment in the majority of the scenarios they rated, 9% (22/254) a preference for PET, and 13% (33/254) an equal preference for surgery and PET. Table 2 summarises the results by scenario.

A response of "no preference" was treated as the reference treatment option compared with "preference for operation" and "prefers PET" using univariate and multivariate analysis. Five of the six variables (age, co-morbidity, cognition, functional status and cancer size) independently demonstrated a statistically signification association with treatment preference on univariate analysis ($p<0.05$). The variable cancer biology (receptor status) was associated with a treatment preference for operation over no preference ($p<0.001$) but not for PET ($p=0.966$) i.e. had a weaker effect on preference than the other variables. However, it should be noted that all options were ER positive so this is not surprising.

On multivariable analysis, functional status had to be omitted from the model due to collinearity; this is most likely due to the close association between this variable and the variables co-morbidity and cognition (e.g. a patient with moderate or severe co-morbidity and or cognitive dysfunction must inevitably also have moderate or severe functional dependence) and so the model could not determine whether an observed effect was due to functional status or co-morbidity/cognition. Table 3 summarises the multivariable analysis results. Overall, all five variables in the model were associated with a preference for operative treatment over no preference. However, only co-morbidity, cognition and cancer size were associated with a preference for PET over no preference.

The goodness of fit of the multivariable model was assessed by the pseudo $R_2$ value. In this case, the pseudo $R_2$ value for the model is 0.31, suggesting this model including these five covariates is better than a model including no covariates by 31%, but is worse than the theoretical perfect fitting model (which would have a pseudo $R_2$ value of 1.0).

The majority of respondents selected treatment in accordance with the patients predicted life expectancy for most scenarios, which is consistent with current guidelines [17]. However in some scenarios, opinion was divided, for example scenarios 3, 4 and 7.

Discussion:

This DCE has confirmed the influence of several predictable factors on HCP decision making in the management of older patients with operable breast cancer. To our knowledge, this is the first application of a DCE in this setting. The results must be interpreted with a note of caution due to the overall response rate of 40% which limits their generalizability, although we can still estimate the preference for different scenarios with a reasonable degree of precision. This rate is lower than the average response rate for postal surveys of doctors quoted in the literature [18], however is comparable with studies conducted on a similar population [19]. Additionally, a limitation of this study, which can be said of any survey methodology, is related to external validity and whether the participants would behave the same way in a real clinical context as they do in the hypothetical scenario.

Recent national guidelines state that patients with operable breast cancer should be treated with surgery, and not PET, "irrespective of age" unless this is precluded by comorbidities [20]; whilst the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) recommend that PET should only be offered to patients with "short estimated life expectancy (<2-3 years), who are considered unfit for surgery… or who refuse surgery" [17]. However, life expectancy is impossible to accurately assess with any certainty, and although considered important by HCPs in determining treatment for older patients with operable breast cancer [12], a recent study has shown that surgeons are poor at gauging life-expectancy of older patients, with a tendency to under-estimate it [21]. Additionally, these current guidelines do not specify which comorbidities may preclude surgery or what constitutes being "unfit" and as such it is left to the treating HCP to determine which patients are considered unsuitable for surgery based on the clinical information available.

Increasing rates of comorbidity with age have been shown to potentially reduce the survival advantage of more aggressive breast cancer therapies [22] and higher levels of comorbidity have been shown to be associated with non-surgical treatment [23]. These results confirm that the degree of comorbidity is a significant factor for HCPs in determining treatment options for older patients with operable breast cancer thus arguably reflecting why comorbidities are often stated as a reason for treating patients with PET [21, 24]

Age also appears to be an independent factor that HCPs consider to be important when making a treatment decision in this population. This being consistent with several studies that have identified a reduction in surgery rates with increasing age for older patients with operable breast cancer [4, 25,

26]. This is most likely due to chronological age often being used by HCPs as a surrogate marker for other factors that are more difficult to quantify, such as life expectancy and frailty [27].

Additionally, dementia, predominantly affecting the elderly, represents a significant problem, though there are currently no guidelines for the treatment of operable breast cancer in this group of patients. Furthermore a recent study demonstrated a lack of consensus among HCPs regarding the optimal way to treat this group [12]. Older patients with dementia are less likely to receive standard cancer therapies [28] and this is often stated as an explanation for selecting PET over surgery [5, 29]. These results confirm that HCPs are less likely to prefer surgery and more likely to opt for PET for patients with moderate and severe cognitive impairment.

Tumour factors were also shown to have an independent influence over the HCPs treatment preference. Larger tumours were associated with lower rates of preference for surgery. This may reflect the fact that larger tumours are more likely to require mastectomy rather than breast conservation surgery and HCPs may wish to avoid more major surgery, although exact tumour size was not specified in the scenarios. Interestingly, preference for surgery significantly increased with increasing ER status but preference for PET did not. This is contrary to what might be expected as response rates for PET are generally higher for patients with greater ER positivity [30]. Additionally, preference for surgery increased for HER2 negative tumours but there was no difference in preference for PET, despite the fact that HER2 positive cancers are known to be generally less likely to respond to endocrine therapy [31]. However, the scenarios only contained limited information on the receptor status and combined ER and HER2 status, without specifying any values, making the results slightly more difficult to interpret. Additionally, the majority of HCPs surveyed were breast surgeons (75.4%) and whilst this type of decision-making is commonly undertaken by the treating breast surgeon in the UK, a different HCP population, for example oncologists, may have yielded different results.

In 2008 the UK's Department of Health established the National Cancer Equality Initiative (NCEI) aiming at lowering the inequality in cancer outcomes for all, including those of older patients [32]. The treatment of older breast cancer patients across the UK is variable, with rates of PET ranging from 10-40% [8]. Healthcare professional recommendation has been shown to be the most influential factor affecting older women's breast cancer treatment decisions [11], and several studies have suggested that variation in treatment may reflect the differing opinions of HCPs so influencing communication of treatment options [10]. This study supports these findings and emphasises the need for evidence-based guidelines on decision-making in this age group.

In conclusion, the majority of HCPs within this study selected treatment in accordance with current guidelines relating to the presence of significant comorbidity. However, in some scenarios, opinion was divided and age did appear to be an independent factor that HCPs considered when making a treatment decision in this population. This study demonstrates that HCP preferences for managing older breast cancer patients are not uniform, which may contribute to the treatment variation seen in this population.

Conflict of Interest: The authors declare no conflict of interest.

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**Figure 1:** Scenario example

| | |
|---|---|
| PATIENT AGE (YEARS) | 85+ |
| CO-MORBIDITY | NONE |
| TUMOUR STAGE | SMALL TUMOUR, NODE POSITIVE |
| BREAST CANCER BIOLOGY | ER++ / HER2- |
| FUNCTIONAL STATUS | MODERATE DEPENDENCE |
| COGNITIVE FUNCTION | SEVERE IMPAIRMENT |

| | | | |
|---|---|---|---|
| For Operation | [ ] | For PET | [ ] |
| Prefer both equally | [ ] | | |

**Please indicate your preferred choice of recommendation for treatment (i.e. in favour of operative treatment or primary endocrine therapy (PET), by placing a tick (✓) in the relevant box below the scenario description. Please assume that each hypothetical patient has asked you to advise them on what treatment option they should choose.**

**Table 1:** Discrete choice variables and levels.

| Variable | Levels | | | |
|---|---|---|---|---|
| **Patient age** | 70-74 | 75-79 | 80-84 | 85+ |
| **Co-morbidity** | None | Mild | Moderate | Severe |
| **Cognition** | Normal | Mild impairment | Moderate Impairment | Severe Impairment |
| **Functional status*** | Independent | Mild dependence | Moderate dependence | Severe dependence |
| **Cancer size** | Small tumour, node negative | Small tumour, node positive | Large tumour, node negative | Large tumour, node positive |
| **Cancer biology** | ER positive, HER2 positive | ER positive, HER2 negative | ER strongly positive, HER2 negative | |

*denotes not included in final model

**Table 2:** Results by scenario (maximum N=254 responders)

| Scenario | Patient Age | Co-morbidity | Cognition | Functional status | Cancer size | Cancer biology | Predicted life expectancy | Preference for PET | Prefer both equally | Preference for Surgery |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 85+ | Severe | Normal | Severe dependence | Small, node negative | ER+, HER2+ | <2 years | 218 (86.2%) | 20 (7.9%) | 15 (5.9%) |
| 2 | 85+ | None | Severe impairment | Moderate dependence | Small, node positive | ER++, HER2- | <2 years | 155 (61.3%) | 66 (26.1%) | 32 (12.6%) |
| 3 | 70-74 | Severe | Normal | Moderate dependence | Large, node negative | ER+, HER2+ | <2 years | 111 (43.9%) | 78 (30.8%) | 64 (25.3%) |
| 4 | 80-84 | None | Moderate impairment | Severe dependence | Small, node negative | ER+, HER2+ | <2 years | 108 (43.0%) | 80 (31.9%) | 63 (25.1%) |
| 5 | 70-74 | None | Severe impairment | Severe dependence | Large, node negative | ER+, HER2- | <2 years | 156 (62.2%) | 65 (25.9%) | 30 (12.0%) |
| 6 | 85+ | Moderate | Moderate impairment | Mild dependence | Large, node negative | ER++, HER2- | 2-5 years | 115 (45.6%) | 104 (41.3%) | 33 (13.1%) |
| 7 | 75-79 | Moderate | Normal | Severe dependence | Large, node positive | ER++, HER2- | 2-5 years | 100 (40.0%) | 95 (38.0%) | 55 (22.0%) |
| 8 | 80-84 | Moderate | Mild impairment | Moderate dependence | Small, node negative | ER+, HER2- | 2-5 years | 39 (15.6%) | 113 (45.2%) | 98 (39.2%) |
| 9 | 85+ | None | Mild impairment | Independent | Large, node positive | ER+, HER2+ | 2-5 years | 20 (7.9%) | 60 (23.8%) | 172 (68.3%) |
| 10 | 70-74 | Mild | Moderate impairment | Moderate dependence | Large, node positive | ER+, HER2- | 2-5 years | 16 (6.3%) | 54 (21.4%) | 182 (72.2%) |
| 11 | 70-74 | None | Normal | Mild dependence | Large, node positive | ER+, HER2- | >5 years | 6 (2.4%) | 14 (5.6%) | 231 (92.0%) |
| 12 | 85+ | Mild | Normal | Independent | Small, node negative | ER+, HER2- | >5 years | 3 (1.2%) | 52 (20.6%) | 198 (78.3%) |
| 13 | 80-84 | None | Normal | Mild dependence | Small, node positive | ER+, HER2- | >5 years | 2 (1.2%) | 39 (15.5%) | 210 (83.7%) |
| 14 | 70-74 | Moderate | Normal | Independent | Small, node positive | ER+, HER2+ | >5 years | 2 (0.8%) | 22 (8.8%) | 227 (90.4%) |
| 15 | 70-74 | None | Normal | Independent | Small, node negative | ER++, HER2- | >5 years | 0 (0.0%) | 2 (0.8%) | 251 (99.2%) |
| 16 | 75-79 | None | Mild Impairment | Independent | Large, node negative | ER+, HER2- | >5 years | 5 (2.0%) | 25 (9.9%) | 223 (88.1%) |
| 17 | 80-84 | Mild | Normal | Independent | Large, node negative | ER++, HER2- | >5 years | 7 (2.8%) | 50 (19.8%) | 195 (77.4%) |

*highlighted area demonstrate respondents overall preference for surgery, PET or both equally by scenario

**Table 3:** Influence of DCE variable over treatment choice (N=248 responders).

| Variable | | Surgery vs equal preference | | | PET vs equal preference | | |
|---|---|---|---|---|---|---|---|
| | Levels | RRR | 95% C.I. | P-value | RRR | 95% C.I. | P-value |
| **Age** | 70-74 | Ref | - | - | Ref | - | - |
| | 75-79 | 0.12 | 0.06-0.22 | <0.001 | 2.05 | 0.88-4.77 | 0.096 |
| | 80-84 | 0.06 | 0.03-0.11 | <0.001 | 2.48 | 0.98-6.25 | 0.055 |
| | 85+ | 0.11 | 0.06-0.19 | <0.001 | 1.84 | 0.78-4.34 | 0.166 |
| | | | | | | | |
| **Co-morbidity** | None | Ref | - | - | Ref | - | - |
| | Mild | 0.67 | 0.46-0.99 | 0.043 | 0.24 | 0.12-0.46 | <0.001 |
| | Moderate | 0.11 | 0.07-0.17 | <0.001 | 0.95 | 0.33-2.74 | 0.923 |
| | Severe | 0.05 | 0.03-0.09 | <0.001 | 20.70 | 8.44-50.73 | <0.001 |
| | | | | | | | |
| **Cognition** | Normal | Ref | - | - | Ref | - | - |
| | Mild impairment | 2.46 | 1.63-3.72 | <0.001 | 0.74 | 0.35-1.55 | 0.424 |
| | Moderate impairment | 0.32 | 0.24-0.42 | <0.001 | 3.67 | 2.07-6.48 | <0.001 |
| | Severe impairment | 0.01 | 0.01-0.03 | <0.001 | 21.45 | 7.01-65.57 | <0.001 |
| | | | | | | | |
| **Cancer size** | Small, node- | Ref | - | - | Ref | - | - |
| | Small, node+ | 1.77 | 1.22-2.56 | 0.003 | 0.18 | 0.09-0.40 | <0.001 |
| | Large, node- | 0.47 | 0.30-0.76 | 0.002 | 0.53 | 0.29-0.97 | 0.039 |
| | Large, node+ | 0.25 | 0.15-0.43 | <0.001 | 1.68 | 0.81-3.44 | 0.161 |
| | | | | | | | |
| **Cancer biology** | ER+,HER2+ | Ref | - | - | Ref | - | - |
| | ER+, HER2- | 1.44 | 1.11-1.86 | 0.006 | 1.41 | 0.76-2.60 | 0.273 |
| | ER++, HER2- | 4.51 | 2.26-8.98 | <0.001 | 2.27 | 0.53-9.72 | 0.269 |

RRR = Relative Risk Ratio