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Title: **HEALTHCARE PROFESSIONALS' PREFERENCES FOR SURGERY OR PRIMARY ENDOCRINE THERAPY TO TREAT OLDER WOMEN WITH OPERABLE BREAST CANCER.**

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Abstract:

Introduction: Primary endocrine therapy (PET) is an alternative treatment to surgery for oestrogen receptor positive (ER+) operable breast cancer in older women. However, there is variable use of PET in the UK, with up to 40% of patients aged over 70 receiving PET instead of surgery in some regions. Treatment options offered to patients rely heavily on healthcare professional (HCP) assessment and opinion on which treatments are appropriate.

Materials and Methods: This was a mixed methods study combining semi-structured interviews with HCPs working in high and low PET regions in the UK, followed by a postal questionnaire survey distributed via the Association of Breast Surgery (ABS).

Results: Thirty-four HCPs (20 breast surgeons; 13 nurse specialists; 1 geriatrician) were interviewed from 14 sites across the UK and 252/641 questionnaires returned (39%). There was an overriding view that PET is not suitable for patients under the age of 80 unless there are significant comorbidities. Opinion was split regarding the best way to treat patients with dementia. Patient preference was generally stated to be the most important factor when considering treatment, however only around a quarter 65/244 (26.6%) felt that all patients over the age of 70 should be offered PET as an alternative treatment option.

Conclusions: Opinions differ on the best way to treat women over 70 with operable breast cancer, especially if they have co-existing dementia, as well as whether they should be offered PET as a treatment option. This may be a significant cause of treatment variation in the UK.

Key words:

Breast cancer, primary endocrine therapy, surgery, elderly, older, mixed methods.

Introduction.

One third of new breast cancer diagnoses occur in women aged over 70 years in the UK [1]. Increasing age results in rising rates of comorbidity and frailty [2] so tolerance to some standard breast cancer therapies may decrease [3] and older patients may prioritise quality of life over quantity [4]. Consequently, older patients with operable breast cancer may be offered alternative treatment modalities, such as primary endocrine therapy (PET) [5, 6], where oestrogen receptor (ER) positive disease is treated with endocrine therapy alone. A meta-analysis comparing PET with surgery found no difference in survival, although rates of local control were inferior with PET [7], which may necessitate a change in management [8, 9]. Case series indicate 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 [10].

Significant cognitive impairment affects up to 20% of women aged between 80-84 years and is associated with a significant reduction in life expectancy [11]. Studies have shown that older women with dementia are less likely to receive surgical treatment for breast cancer [12]. Currently, there are no data on how this impacts on cancer outcomes in this group of women and therefore what best practice should be.

National audits have demonstrated significant variation in the use of PET across the UK [13] which is not fully explained by case mix variation (stage, deprivation, etc.) [14]. Clinician preference has been suggested as a possible explanation for some of this variation [15]. To date, there is little in the published literature examining how healthcare professionals (HCPs) determine which older patients should be offered surgery, PET or a choice of both as treatment for operable breast cancer. This study aimed to determine what factors are important to HCPs when determining what treatment options to offer older patients with operable breast cancer and to explore their views and experience on the use of both surgery and PET in this population.

Materials and Methods:

University of Sheffield Research Ethics Committee and local institutional approvals were obtained (SMBRER243). The study followed an exploratory sequential mixed methods design [16] (see figure 1), using semi-structured qualitative interviews to initially explore and document the views and experiences of HCPs on the treatment of older women with operable breast cancer. The themes raised in these interviews then informed the development of a survey-style questionnaire to quantify the importance of these themes.

Semi-structured Qualitative Interviews.

Purposive sampling of HCPs (including breast surgeons, specialist nurses and geriatricians) from regions of high and low PET rates across the UK was performed. PET rates for each unit were derived from UK Registry data [13]. Semi-structured interviews were undertaken at the workplace of the individuals and written consent was obtained. Interviews were digitally recorded and transcribed verbatim. Recruitment ceased once data saturation had occurred. Analysis was performed using the National Centre for Social Research "Framework" approach to identify themes within the data [17].

Quantitative Postal Questionnaire Survey.

A postal questionnaire was designed based on the relevant literature and using the themes identified in the qualitative interviews, to maximise content validity. Face validity and acceptability were assessed during a pilot phase with 5 HCPs. The survey 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. All analyses were performed using IBM SPSS Statistics version 21.

Results:

Semi-structured Qualitative Interviews.

Forty two HCPs were invited to interview and 34 agreed to be interviewed from 14 of the UK's 166 breast cancer units. Participants comprised of 20 surgeons (10 male, 10 female), 13 BCNs (all female), and 1 geriatrician (male). The mean duration of interviews was 33 minutes (16-55). Twenty-one (62%) were from high PET units, with the remaining 13 from low PET units. There were no differences in characteristics between HCPs who took part and those that declined.

Thematic analysis categorised data into three main themes summarising HCPs opinions on the use of surgery and PET in the management of older patients with operable breast cancer. These are summarised in Table 1 with representative quotes.

Quantitative Postal Questionnaire Survey.

Of the 641 questionnaires distributed, 251 were returned (39% response rate). See Table 2 for characteristics of respondents.

Views of HCPs to treating older women with operable breast cancer.

A key theme to emerge from the interviews was the importance of determining whether an older woman was fit for standard treatment i.e. surgery:

> *"You're trying to work out: are they fit enough"* (Female nurse; high PET rate)

Most said that age was not a factor when deciding treatment, and that other factors such as level of comorbidity, frailty and life expectancy, were more important.

> *"You give the patient treatment that the cancer deserves and not an age deserves… I would never differentiate on age because I wouldn't want that to be done to me and so why would I do it to someone else?"* (Male surgeon; low PET rate)

This seemed specifically to be the case when clinicians weighted various factors according to their importance (see Figure 2).

Additionally, HCPs seemed to feel that the definition of "old" had increased:

"I would say 70's not really my cut off now, it's more like 80… This kind of drive to do more surgery for elderly patients has actually raised the definition of 'elderly' from 70 to 80. I think we're now dealing with the same questions but with a population of 10 years older" (Male surgeon; low PET rate)

The presence of comorbidities was the most important factor when HCPs considered whether or not they determined an older woman to be fit for surgery with all respondents 248/248 (100%) rating this factor as having at least some importance (see Figure 2); and nearly two thirds (155/246; 63.0%) agreeing with the statement "All women ≥70 with operable ER+ breast cancer, who have multiple comorbidities such that anaesthesia may carry an increased risk of morbidity and mortality, should be treated with PET".

Significant dementia had a major impact on HCP treatment recommendations, with 102/248 (41.1%) agreeing with the statement "all women ≥70 with operable ER+ breast cancer, who have significant dementia (unable to give informed consent) should be treated with PET". In terms of relative importance, 89% rated the presence of dementia as very important or important in making treatment decisions.

Experience of surgical treatment in older women with breast cancer

Surgery was generally considered to be the superior treatment option for older women with operable breast cancer:

"I'm of the opinion that surgery is the gold standard" (Female nurse; high PET rate)

Over three quarters (199/249) of respondents agreed with the statement "All women ≥70 with operable breast cancer should be offered an operation regardless of age". Furthermore 241/245 (98.4%) of HCPs stated that in their experience, surgery under GA was well tolerated in older women. However, experience with the usage of local anaesthetic (LA) and regional techniques was more variable, with only 43/244 (17.6%) stating that they had an anaesthetist who would happily perform regional blocks to allow surgical excision in patients where GA may carry an increased risk. Despite this, 156/244 (63.9%) felt that surgery under LA was well tolerated in older women and 148/246 (60.2%) agreed with the statement "surgery is almost always possible for older women ≥70 with operable breast cancer under local or regional anaesthesia".

Stage and size of the disease was viewed as being less important in determining treatment than patient health and fitness measures (see Figure 2) as although more than 87.4% (216/247) rated this

as of at least some importance, only 22.7% (56/247) regarded it as very important. Axillary disease was rated as slightly more important with 27.5% (68/247) rating it as very important. ER status was regarded as important or very important by most surgeons (216/248; 87.1%) but HER2 status much less so (123/245; 50.2%).

Assessment of older patients for surgery also varied, with some HCPs using formal Comprehensive Geriatric Assessments (CGAs), others relying on their anaesthetic colleagues to guide them and many using simple assessments, such as whether the patients can walk up a flight of stairs, to determine their fitness (see table 1).

Experience of PET as a treatment in older women with breast cancer

Primary Endocrine Therapy was generally regarded as the inferior treatment option by HCPs

> *"Primary Endocrine Therapy alone probably long-term is not as good an option"* (Female surgeon, high PET rate)

With 65/244 (26.6%) agreeing that PET may be offered to any older woman with ER positive disease as there is no proven survival advantage. There was a strong view (217/247; 84.6%) that older women, if given the choice between PET or surgery, would choose surgery.

Despite this, PET is still used to treat women across the UK, although its use is variable, with 17/240 (7.1%) stating that more than 30% of women ≥70 were treated this way, 65/240 (27.1%) stating that 20-30% of women ≥70 were treated with PET, 67/240 (27.9%) stating that 10-20% of women ≥70 received PET and 91/240 (37.9%) stating that PET was used in less than 10% of women ≥70 years.

There was variation regarding how long HCPs felt that PET was effective in maintaining local tumour control, with 64/238 (26.9%) stating 5 years or more; 74/238 (31.1%) stating 3 years, 70/238 (29.4%) stating 2 years and 30/238 (12.6%) stating 18 months or less.

From the interviews, it was identified that most HCPs used aromatase inhibitors (AIs) as first line PET and this was usually Letrozole, although one commented that they used Tamoxifen and a couple used Anastrazole as first-line. Additionally, follow-up varied significantly between units (see table 1) and opinion was divided regarding what action to take if first-line anti-oestrogen failed to achieve a response, with 146/245 (59.6%) opting for a second-line anti-oestrogen, 61/245 (24.9%) advising operative management, 4/245 (1.6%) opting for radiotherapy and 34/245 (13.9%) stating that they would consider more than one of these options.

Discussion:

The use of PET for the treatment of older breast cancer patients across the UK is variable [13] and this study supports these findings. Over a third of respondents stated they treated more than 20% of this population with PET, even though it was generally considered to be the inferior treatment option, with surgery as the 'standard'.

In 2008 the UK's Department of Health established the National Cancer Equality Initiative (NCEI) aimed at lowering the inequality in cancer outcomes for all, including those of older patients [18]. Recent guidelines suggest that PET should only be offered to patients with a "short estimated life expectancy (<2-3 years), who are considered unfit for surgery… or who refuse surgery" [19]. However, they do not provide guidance regarding what constitutes being 'unfit' for surgery, and life expectancy is impossible to accurately assess with any certainty. As such it is left to the treating clinician to determine treatment, resulting in a wide variation in practice.

Increasing age is associated with higher rates of comorbidity, which has been shown to potentially reduce the survival advantage of more aggressive breast cancer therapies [2]. Comorbidities are often stated as a reason for treating patients with PET [9, 20] and our results show that the presence of comorbidities was the most important factor HCPs considered when deciding treatment options for older patients with operable breast cancer.

Life-expectancy was also considered relatively important however a recent UK questionnaire study found that surgeons are poor at gauging life-expectancy of older patients, with a tendency to under-estimate it [20]. Older patients have a reduced life expectancy, with the average 75-year-old woman expected to life 13.5 years compared to 5.0 years for an average 90-year-old [21]. As such chronological age is often used by clinicians as a surrogate marker life expectancy and other factors, such as comorbidity and frailty [22].

Several studies have explored the issue of increasing age being associated with "under treatment" of older women with operable breast cancer [5, 23-25]. Our results show that whilst HCPs consider age one of the least important factors in determining which treatment options to offer, it remains important and several interview participants admitted to using age-specific cut-offs to determine who should be offered PET.

Tumour factors were considered less important in treatment decision-making than patient factors, even though larger tumours are more likely to require mastectomy rather than breast conservation surgery. Nodal status was considered slightly more important and this may be due to the fact that surgery to clear the axilla under local anaesthesia is not technically possible and therefore surgery to

clear an involved axilla would be precluded in women who were too frail to undergo GA. Despite the fact that HER2 positive cancers are known to be generally less likely to respond to endocrine therapy [26], it was considered much less important than ER status.

There was a strong view that older women, if given the choice, would choose surgery over PET. Whether this statement's response would have changed had the questionnaire contained a different age cut-off we are unable to confirm but current UK practice, combined with the findings that the definition of "old" has increased, would suggest this to be the case.

This study identified major variation in the way PET is used in respect of the type of first-line anti-oestrogen prescribed, the assessment methods and follow-up regimen used. This corroborates the findings by Wylie et al [20] and is most likely due to a lack of guidelines on its usage. A recent review on this subject advocates the use of AIs for PET, unless otherwise contraindicated [27] but there have been no studies that determine how best to follow these patients up. The involvement of geriatricians and the use of CGA in the assessment of older patients is also recommended [19], however few HCPs had access to this type of service.

The major drawback of PET is the risk of development of progressive disease which most patients will eventually suffer [28] although the length of time to progression varies greatly from nine to 132 months [29-33]. The duration of response is generally shorter in women who have only exhibited a partial response to PET, compared to those with a complete response [31, 34]. This may explain why there was so much variation in HCP opinion as to how long PET maintains tumour control.

Evidence suggests that elderly patients may prioritise quality of life over quantity [4] and patient choice is commonly stated as a reason for treating patients with PET [10, 20]. However, a recent study by Lavelle and colleagues [23] found that lower rates of surgical treatment are unlikely to be due to patient choice and these results suggest that UK HCPs agree with this, believing that patients would not choose non-operative management if given the option. Hamaker and colleagues [15] suggested that variation in treatment may reflect underlying clinician preference influencing communication of treatment options. This seems a plausible explanation, especially in view of Schonberg and colleague's findings that the most influential factor affecting older women's breast cancer treatment decisions was the surgeon's recommendation [35]. Indeed, this study demonstrates multiple areas of variation in HCP opinion supporting this.

Around a quarter of HCPs agreed that PET may be offered to any older woman with ER positive disease as there is no proven survival advantage, which is more than three times the number found by Wylie et al [20]. Shared Decision-Making (SDM) suggests that patients should be informed of their

treatment options [36] and for some older women it may be appropriate to offer PET as an alternative to 'standard' surgical treatment and allow the patient to decide what is best for them. However, not all older patients engage in SDM, with many preferring a more passive role [35, 37-39], which may be reinforcing the variation due to clinician preferences.

For those older breast cancer patients who are unable to make a decision due to significant dementia, opinion was divided regarding the best treatment approach. With dementia predominantly affecting the elderly, this represents a significant problem in this population. Studies show that older patients with dementia are less likely to receive standard cancer therapies [12] and that this is often stated as a reason for selecting PET over surgery [6, 40]. However, there are currently no guidelines for the treatment of operable breast cancer in this complex group of patients which may reflect the lack of consensus amongst HCPs surveyed here. A further explanation for such differing views may be that dementia was not defined in the survey, and HCPs clinical judgement of dementia may vary in the absence of formal assessments.

The use of local and regional anaesthesia for breast surgery in patients who are unable to undergo GA is well-established [41], with nearly two thirds of respondents feeling that surgery in older patients was well-tolerated under LA. However, it seems that a limiting factor in the utilisation of regional techniques is the availability of a suitably-experienced anaesthetist.

Limitations of this study include the low response rate to the questionnaire, although this is comparable with other similar studies [20, 42], but limits the generalizability of the results. Additionally, it has previously been shown that most UK breast surgeons do not formally audit their practice in terms of PET [20] and so will have had to have estimated in some areas, such as the percentage of patients treated with PET. However the mixed methodology means that the questionnaire results complement and build on those from the interviews, giving a broader picture of this topic.

In conclusion, HCP opinions differ on the best way to treat older women with operable breast cancer, especially if they have co-existing dementia, and whether they should be offered PET as a treatment option. This may be a significant cause of the variation in treatment of older women with breast cancer in the UK and highlights the urgent need for evidence based guidelines for decision making in this age group.

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Conflict of interest statement

The authors declare no conflict of interest.

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Figure 1: The sequential exploratory mixed methods study.

Abbreviations: QUAN = quantitative; QUAL = qualitative.

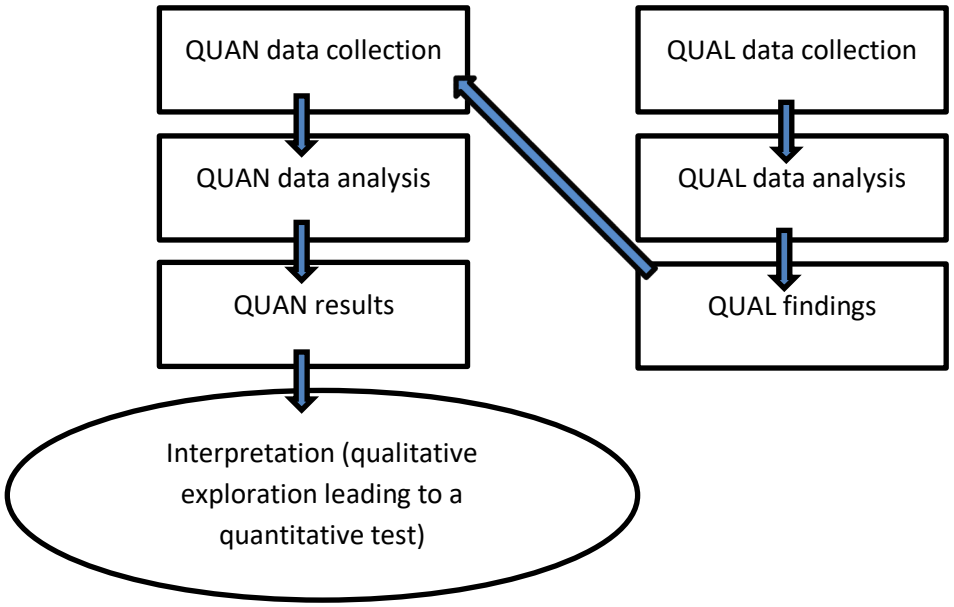

Figure 2: Patient and tumour characteristics and their importance in shaping the advice HCPs would give to an older patient in whom a choice of PET and surgery may be considered (n=252).

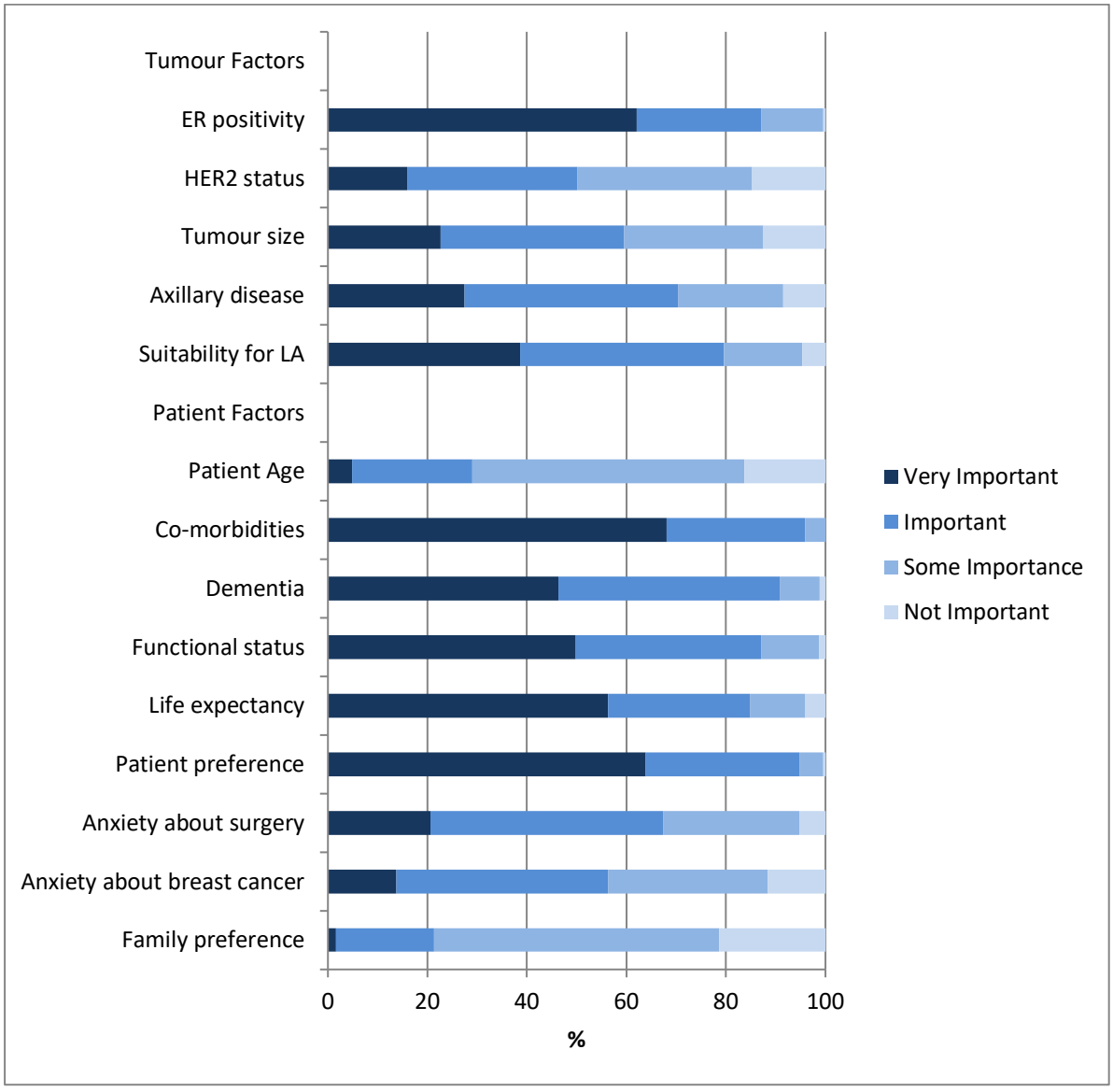

Table 1: Qualitative Themes with representative quotes.

Theme	Healthcare Professional Quotes
Approach to treating older women with operable breast cancer	
Impact of age on the	Age as a factor in deciding treatment: *"Age is irrelevant really isn't it, it should be"* (Nurse, high)

treatment of breast cancer	*"Once they get to 85 and above, then I would be certainly talking to patients about PET in equal terms as surgery… between 70 and 80… we'd really want them to be having surgery"* (Surgeon, high)
	Inherent biases towards older patients: *"Everyone does take age into account, and you can't help it"* (Surgeon, high)
	The definition of old has changed: *"This drive to do more surgery for elderly patients has actually raised the definition of 'elderly' from 70 to 80"* (Surgeon, low)
Factors influencing treatment in older patients	Fitness for surgery: *"Often boils down to… is this patient fit for standard treatment"* (Surgeon, high)
	Dementia: *"Dementia is the one indication for PET in my book"* (Surgeon, low) *"These patients need double consenting and surgery"* (Surgeon, low)
	Life expectancy: *"If you've got… a predicted survival of less than two to three years there's no additional benefit from surgery"* (Surgeon, high)
	Frailty: *"I'm sure there are those who come, looking frail… and we just go 'have this nice tablet' "* (Surgeon, high)
	Patient preference: *"Patient views obviously have the primacy"* (Surgeon, high)
Assessment of older patients	End of the bed assessments: *"There's a lot of patients you can eyeball, if they can go up a flight of steps… you know they'll be ok for a GA"* (Surgeon, low)
	Anaesthetic assessment: *"Let's put the actual risk of an anaesthetic into the mix"* (Surgeon, high) *"Then we leave it to the anaesthetists to decide"* (Surgeon, low)
	Use of comprehensive geriatric and frailty assessments: *"I don't do a CGA at the moment"* (Surgeon, high) *"It is mandatory to have frailty assessments… if you don't… you are biased in an ageist decision which is not evidence-based"* (Surgeon, low)
Variation in treatment of older patients	Idea of over-treatment: *"may be more treatment than she actually needs"* (Surgeon, high)
	Elderly are a heterogeneous group of patients: *"You've got your tennis playing 75, 78, 80 year olds and you've got your decrepit 71 year olds"* (Surgeon, high)
	Tailoring treatment to the individual: *"Important that we offer them the appropriate treatment, tailored to that patient – one size does not fit all"* (Surgeon, low)
	Reasons for variation: *"I've got a feeling that we should blame the healthcare professionals more rather than the patients"* (Surgeon, high) *"Ladies are not given the choice I would have to argue or it's not given in a… non-biased way"* (Nurse, high) *"Although it looks on paper that people are treating older women differently, sometimes it's a lot of patient choice"* (Nurse, high)
Experience of surgical treatment in older women with breast cancer	
Views on surgery as a	Surgery is the superior treatment option: *"Surgery is the gold standard"* (Nurse, high)

treatment for older patients	Surgery is considered safe: *"Surgery is very safe nowadays"* (Surgeon, high)
Pros and cons of surgical treatment for older patients	*"Better local control"* (Surgeon, low)
	Can be performed as a day case: *"Their dog can be walked the day after because it's a day case procedure"* (Surgeon, low)
	Recovery may not be as straightforward in the elderly: *"A complication… causes a much bigger set-back and a much bigger impact on their quality of life"* (Surgeon, high)
	Impact of cosmesis: *"Some people are traumatised by having their breast off"* (Nurse, high) *"At that stage of life most women are less concerned about disfigurement"* (Surgeon, low)
Perceptions of older patients views of surgery	*"They're fearful of surgery"* (Nurse, high) *"Patients' perceptions about the risks are completely different from the actual risk"* (Surgeon, low) *"I think a lot of the patients who go for surgery… they are pleasantly surprised about how well they are afterwards"* (Nurse, high)
Older patients who refuse surgery	*"At that age, they are not very keen to go for surgery"* (Surgeon, high)
	Variable response to refusal: *"They are the ones I would like to persuade towards surgery"* (Surgeon, low) *"I will accept their decision & put them on hormone therapy"* (Surgeon, high)
Use of local anaesthetic surgery	Variable use of local anaesthetic surgery: *"Majority of my elderly pts will have their wide local excision under local"* (Surgeon, low) *"You can do a wide local under local anaesthesia... it doesn't seem to be something we do"* (Surgeon, high)
Experience of PET as a treatment in older women with breast cancer	
Views on PET as a treatment in older patients	*"I feel… PET is writing somebody off"* (Surgeon, low) *"It does seem to be a fairly long-term good treatment"* (Nurse, high)
	PET only offered to certain patients: *"Should be reserved for people who will struggle to get through standard treatment"* (Surgeon, high) vs. offering it to all patients: *"I offer both treatments* (surgery and PET) *to all pts"* (Surgeon, low) vs. not offering it to any patients: *"I see endocrine therapy as adjuvant, and sometimes neo-adjuvant but I don't see it as a standalone treatment"* (Surgeon, low)
Pros and cons of PET as a treatment for older patients	*"Endocrine therapy in oestrogen receptor positive women can be very effective at controlling the cancer"* (Surgeon, high)
	"It avoids them coming into hospital, having an operation, avoids radiotherapy" (Surgeon, high)
	Issues of compliance: *"You're relying on them to actually take it"* (Nurse, high)
	"Endocrine therapy is going to stop working, and they're going to be a couple of years older, maybe not fit for surgery at that point" (Nurse, high)
Perceptions of older patients views of PET	*"They don't like the idea that they still have a cancer within the body"* (Nurse, high)

	"I've never had an instance where a patient has said to me 'no I'm fine, I'll have the tablets' and then… later on 'I don't like this lump here' " (Nurse, high)
Practicalities of treating older women with PET	Variation in type of PET used: *"It's generally Letrozole for PET"* (Nurse, low) *"You're better off just giving them Anastrozole"* (Surgeon, high) *"If somebody has had… thromboembolic events… obviously we put them on Letrozole. If not Tamoxifen"* (Surgeon, low)
	Variation in tumour assessment: *"Scanning them every 6 months"* (Surgeon, low) *"I measure it by eye"* (Surgeon, low) *"I tend to use a bi-dimensional caliper measurement"* (Surgeon, high)
	Variable response time: *"Some women obviously go a long time on endocrine therapy and others don't even get that first response"* (Nurse, high)
	Variable reaction to loss of control: *"Sometimes we change the tablet"* (Surgeon, high) *"If they're non-responders... would re-explore the surgical option"* (Nurse, low) *"Surgery may not then be an option and you've only got radiotherapy"* (Nurse, high)

Abbreviations: High = high PET rate unit; Low = low PET rate unit.

Table 2: Characteristics of questionnaire respondents.

Characteristic		n (%)
Age	Median 50 years Range 28-69 years	
Sex	Male	115 (45.6)
	Female	134 (53.2)
Profession	Breast surgeon	190 (75.4)
	Clinical nurse specialist	55 (21.8)
	Oncologist	2 (0.8)
	Breast physician	1 (0.4)
	Plastic surgeon	2 (0.8)
Region (based on UK cancer registration regions)	Eastern	26 (10.3)
	North West	23 (9.1)
	Northern & Yorkshire	37 (14.7)
	Northern Ireland	6 (2.3)
	Oxford	5 (2.0)
	Scotland	20 (7.9)
	South West	37 (14.7)
	Thames	42 (16.7)
	Trent	14 (5.6)
	Wales	14 (5.6)
	West Midlands	22 (8.7)