# Primary Endocrine Therapy

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Jenna Morgan and Lynda Wyld

**Abstract**

Use of endocrine therapy alone for the treatment of operable breast cancer, (primary endocrine therapy or PET) was first described in the 1980s and is a strategy adopted to varying degrees by different countries. It is a good option for the very frail or unfit older women with ER positive breast cancer. Selection for its use must take into account the probable life expectancy of the woman because secondary antioestrogen resistance develops after a median of 2–3 years. The biology of the tumour has a strong influence on response rates and aromatase inhibitors perform better than tamoxifen in this setting. Primary endocrine therapy is well tolerated and may avoid unnecessary morbidity for some women if selected appropriately. At present there are no evidence based selection guidelines but it is hoped these will be published soon once the Age Gap trial reports.

**Keywords**

Surgery · Primary endocrine therapy · Outcomes · Risk assessment

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## 5.1 Introduction

It has been known for over 100 years that removing the ovaries will result in breast cancer regression in some cases. The true underpinning biology of this phenomena was not understood until the 1960s when oestrogen receptors (ER) were identified on breast epithelial cells [1].

Tamoxifen was developed by Arthur Walpole, in 1962, initially being developed as a contraceptive. It was rapidly adopted into the armamentarium of breast cancer therapy, initially in the 1970s in the advanced [2] and later, in the 1980s, in the adjuvant setting [3].

In 1982, Preece and colleagues suggested that for older women surgery might be avoided completely by use of tamoxifen as sole therapy for operable breast cancer [4]. Five year follow up of a cohort of 113 older women, of whom 76% showed an initial clinical response, found that in 62% of cases tamoxifen alone did not control disease until death or latest follow up and they advocated PET only be used as a short term measure or in the very frail [5]. This would permit selective avoidance of surgery in frailer older women at a time when anaesthesia and surgery risks were greater than they are today. In the subsequent decade several randomised trials (RCTs) were conducted which showed that when compared to surgery, tamoxifen PET was associated with no overall survival disadvantage on 5 year follow up on meta-analysis, but there was a reduction in progression or recurrence free survival [6] (Fig. 5.1).

At the time that these studies were performed testing for the presence of oestrogen receptors on tumours was not routinely performed and therefore 15–20% of the enrolled women will have been effectively taking placebo, which may have skewed the results in favour of surgery.

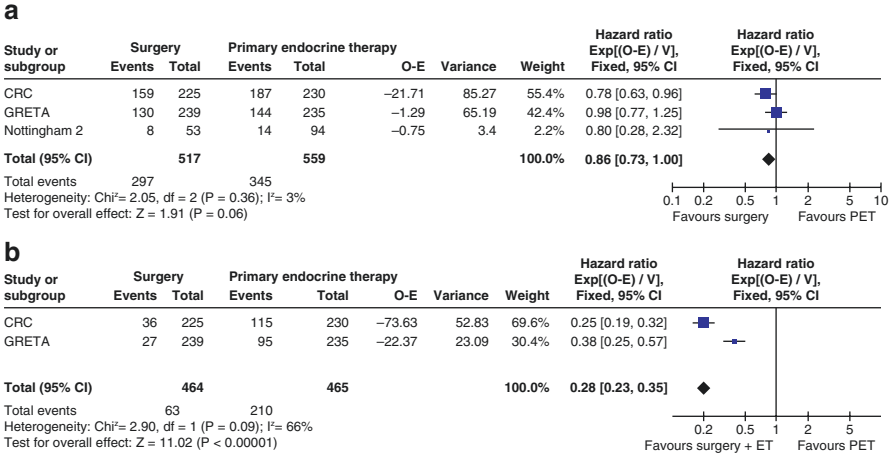


**Fig. 5.1** (**a**) Forest plots comparing overall survival after surgery (plus adjuvant endocrine therapy) versus primary endocrine therapy. (Both reproduced with permission from Morgan et al. [6]). (**b**) Forest plots comparing local disease control after surgery (plus adjuvant endocrine therapy) versus primary endocrine therapy

The data in these studies changed practice in some countries and there was a shift away from surgery for women over 70 with early breast cancer. In the UK, up to 40% of older women were treated with PET in some series [7, 8]. A decade after this shift, when longer term follow up of these trials was published [9], clinicians began to realise that fitter older women were disadvantaged by PET. The CRC trial found a hazard ratio (after 13 years of follow up) for overall survival of 1.29 (1.04–1.59) and breast cancer specific survival of 1.68 (1.15–2.49) for older women who had surgery. For those treated with PET, a change of management was often required, with 40% requiring subsequent surgery and others requiring a change of antioestrogen. A more sophisticated approach was required based on assessment of the biology of the tumour, the age and fitness of the patient and giving the woman a role in making the decision herself based on her personal priorities.

Unfortunately, a more sophisticated approach is not yet a reality and rates of non-surgical treatment are still high [10]. There are presently no age and fitness stratified evidence-based guidelines about who may benefit from surgery and who may safely avoid it.

Predicting life expectancy is not an exact science and is not part of routine clinical practice for surgeons as it requires a lengthy assessment, which time constraints in many Units preclude, even if the technical expertise is present.

The following sections review various aspects of PET in present day practice.

## 5.2 Variation in Use of Primary Endocrine Therapy

Use of primary endocrine therapy is heterogeneous between countries, breast units and surgeons. Derks and colleagues compared rates of non-surgical therapy and found a rate of 28% in the UK, (the highest) versus 9% in Poland [11]. In the USA it is rarely, if ever, used [12]. It has been suggested that this may be one of the reasons for the inferior outcomes seen in older women with breast cancer in the UK [11]. There is also wide variation in the use of PET within the UK with rates of surgery varying between 50% and 90% (Fig. 5.3) [10]. This variance persists after case mix adjustment (for deprivation, age and fitness levels, Fig. 5.2) and likely represents variation in surgeon preference [13]. This is despite current guidelines from several national and international bodies. The National Institute of Health and Care Excellence (NICE) states that PET should only be used if "significant comorbidity precludes surgery" [14]. The International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) recommend 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" [15].

Some units operate on almost every older woman, even those with very poor life expectancy, whereas others offer PET to older women regardless of their level of fitness (Fig. 5.2).

Similarly rates of PET vary between surgeons with some operating on almost all women and others the reverse [13]. Thresholds for offering surgery vary between surgeons as shown by the results of scenario based research where widely different

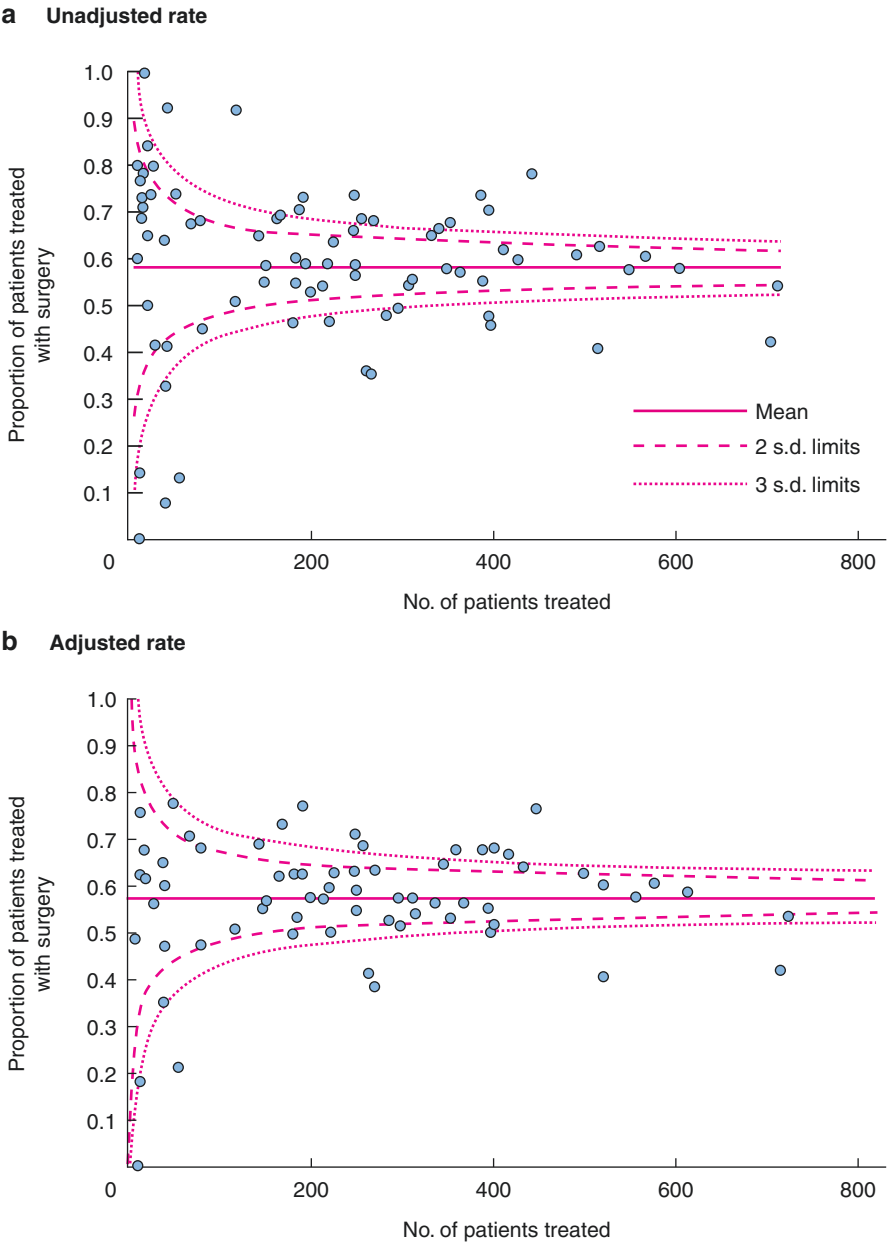


**Fig. 5.2** Funnel plots showing case mix adjusted (**a**) and unadjusted (**b**) rates of surgery for older women with ER+ cancer based on UK registry data analysis. (Reproduced with permission from Morgan et al. [13]). Factors adjusted for were age, comorbidity, deprivation quintile, method of cancer detection, tumour size, stage, grade and nodal status

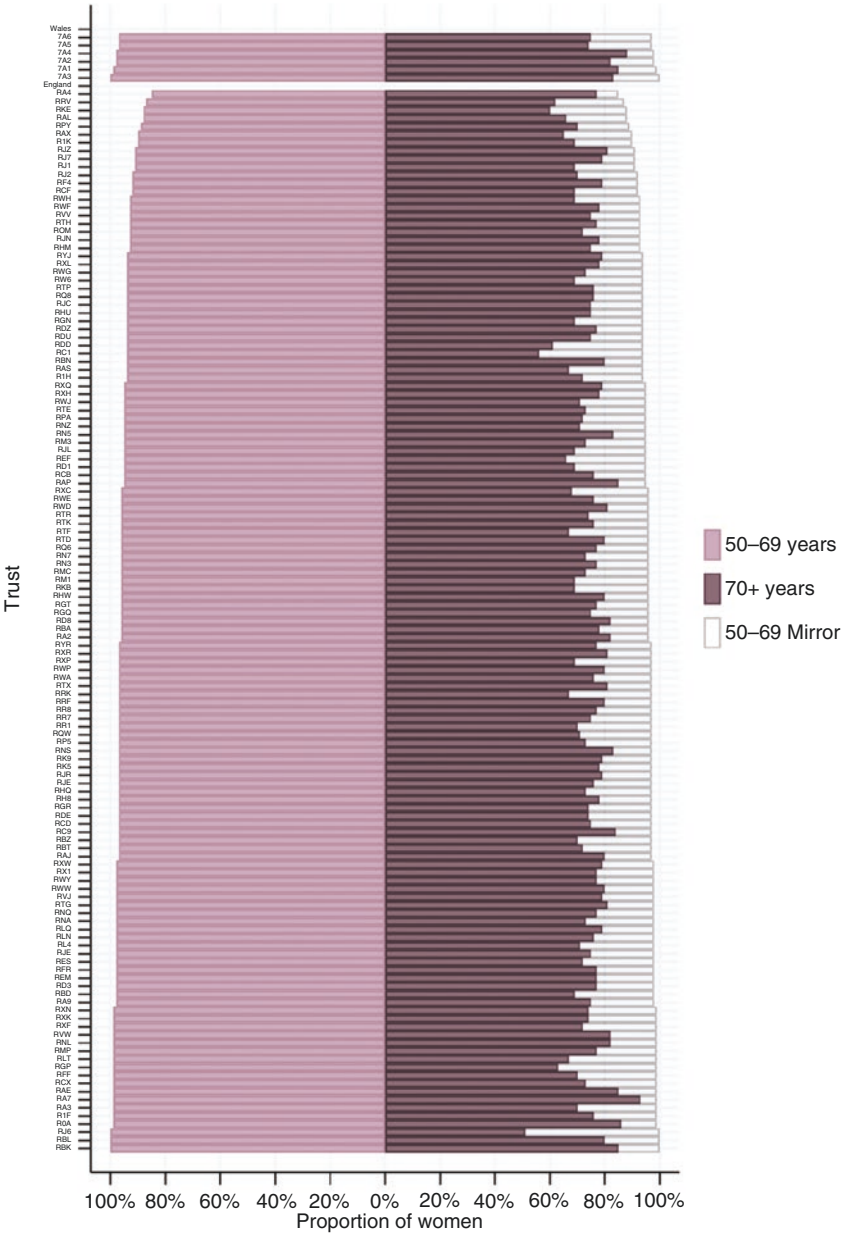


**Fig. 5.3** Risk adjusted proportion of women receiving primary surgical treatment for early invasive breast cancer by diagnosing treatment centre and age at diagnosis. (Reproduced with permission from [10]). **Note:** Figure ordered by country of diagnosis and then Organisation-specific proportions receiving primary surgical treatment in women aged 50–69 years at diagnosis. The "50–69 Mirror" bars are the reflection of the proportions for the 50–69 age group over the proportions for the 70+ age group, to aid comparison

preferences have been demonstrated between surgeons for any given set of age/fitness/frailty characteristics of a patient [16, 17]. It is thought that inappropriately low rates of surgery may contribute to inferior breast cancer outcomes in older women [11] (Fig. 5.3).

## 5.3 Clinical Response to Primary Endocrine Therapy

Primary endocrine therapy does not usually result in rapid tumour regression as is typical of neoadjuvant chemotherapy. In most cases, whilst tumour softening may be seen at 6 weeks, tumour shrinkage is unlikely to be apparent until 3–6 months and the response may continue to improve for 9–12 months or more until maximal response is achieved. Responses are usually graded as either complete response (CR), partial response (PR), static disease (SD) or progressive disease (PD). A combined measure of response, the clinical benefit rate, is the sum of CR, PR and SD. The breakdown of response achieved in PET in reported studies is shown in Table 5.1 (modified from Morgan et al. [18]).

Assessment of response may be by clinical measurement or by imaging, depending on unit protocol and the ease of clinical assessment of a particular tumour. It is important that the same method is always used at each visit as there is variation between US, mammographic and clinical measurements. In modern practice, PET is only offered to women with ER positive tumours. De novo disease progression is indicative of primary antioestrogen resistance. Over the longer term, initially responsive disease acquires secondary resistance, the rate of which varies according to the length of follow up. Failure rates (both primary and secondary) vary between studies, with rates reported between 37% and 84% in studies with median follow up durations of 76 and 70 months respectively [22, 28].

**Table 5.1** Summary of percentage tumour response from clinical trials of Tamoxifen or aromatase inhibitor PET in older patients. (Clinical benefit rate is CR + PR + SD). All tumours confirmed as ER+ in these studies

| Study | Number of patients | PET Type | Clinical benefit rate | Complete response (CR) | Partial response (PR) | Static disease (SD) | Progressive disease | Median duration of follow up months (range) |
|---|---|---|---|---|---|---|---|---|
| [19] | 59 | Tam | 54 | 24 | 22 | 8 | 34 | >6 |
| [20] | 62 | Tam/AI | 60 | – | – | – | – | 20(2–150) |
| [21] | 84 | Tam | 100 | 8 | 18 | 74 | 0 | 24(6–72) |
| [22] | 70 | Tam | 77 | – | – | – | – | 70(9–119) |
| [23] | 104 | AI | 82 | 23 | 40 | 18 | 18 | 56(4–106) |
| [24] | 616 | Tam/AI | 84 | 26 | 30 | 29 | 16 | 41(1–202) |
| [25] | 91 | Tam/AI | 76 | 17 | 45 | 16 | 16 | 18(2–70) |
| [26] | 56 | AI | 100 | 11 | 77 | 13 | 0 | 51(19–78) |
| [27] | 56 | AI | 100 | 25 | 52 | 23 | 0 | 12 |

Modified from Morgan et al. [18]

Clinical factors which predict a good quality and long duration of response include a small initial tumour size and a good early clinical response. Women with static disease at their 3–6 month assessment are less likely to have good long-term disease control than women with complete, or partial response, with initial complete response being associated with a 50 month response duration, partial response 18 months and static disease 21 months [5].

There is a correlation between early stage disease and good response, with one study reporting a 100% clinical benefit rate for stage 1 disease, 83% for stage 2 disease and 66% for stage 3 disease [5]. Other studies have shown similar findings, with only a 53% response rate in T4 tumours compared to an 80–86% response in T2 and T3 disease [29].

The time taken to reach a best response is quite variable, ranging from 3 to 37 months, with a median of 9 months [5]. In fact for women who have an initial complete response, up to 90–100% will still be controlled at 5 years in some studies [5, 30]. Others studies have shown less favourable results, with only 42% of complete responders in remission at 47 months, but the range of response duration was from 5–96 months in this study, which included a high (47%) proportion of T4 tumours [29].

In terms of the long-term rate of local control, most studies report that local disease progression, requiring a change of management, occurs in between 32 and 62 percent of women. One trial with very long follow up (12 years) (Fennessy et al. [9]), found a failure of local control rate of 53.4%, with the median time for failure to occur at 1.69 years (range 1.43–1.82 years). This was substantially worse than women in the surgical arm of the trial, where local failure occurred in only 15.6% of women. Most of these local failures were treated with surgery (64%), with 29% having a change of hormonal therapy or radiotherapy (19%). As with most of the studies of PET, these data have to be viewed in the knowledge that they do not mirror current PET practice, as approximately 20% of all patients will have had ER negative cancers, and will have thus progressed on PET inevitably and effectively had a delay in starting any effective therapy for a significant period. Secondly, in view of the knowledge accrued from these studies, most (but not all) clinicians would reserve PET for older and frailer women (unlike most of the trials, which recruited women aged over 70 regardless of their health status).

### 5.3.1 Biological Predictors of Response

Prediction of endocrine responsive breast cancer is increasingly complex although most of our understanding comes from neoadjuvant endocrine therapy where down staging prior to planned surgery is the aim, rather than in the PET setting in the frail elderly. There is now a greater understanding of the molecular biology of primary and secondary endocrine resistance and increasingly sophisticated tools to predict response. The subject is complex as most tumours are genetically heterogeneous at diagnosis. Matters are further complicated by tumour evolution during treatment which may select out certain resistant clones, new mutations may occur and gene

expression may be altered [31]. Simple loss of expression of the ER is an uncommon mechanism of antioestrogen resistance which is more commonly caused by changes in the down-stream regulatory pathways such as the PI3K/mTOR signalling pathway or cell cycle regulatory mechanisms [32]. Therefore, use of alternate antioestrogens, potentially combined with other agents to target specifically these downstream pathways, has potential to overcome resistance.

In current clinical practice two biomarkers are usually used in the prediction of response: the ER and Her-2 receptors. Tumours which have higher ER scores are more likely to respond well and for a long duration than ER poor tumours and may do as well with surgery as with PET in some series [24] and conversely HER-2 positive tumours are more likely to develop antioestrogen resistance, especially to tamoxifen.

However more sophisticated predictive biomarkers are available or under development in the adjuvant, neoadjuvant or advanced setting. None of these technologies have been evaluated in the PET setting with the exception of tissue biopsy after treatment. These may be classified as multigene arrays or treatment response markers (based on either rebiopsy of the tumour after treatment or monitoring of circulating tumour cells or DNA on blood samples).

In the neoadjuvant setting use of one multigene array, Oncotype DX®, in women on exemestane for 6 months before surgery found that a low recurrence score correlated with a higher chance of clinical response and conservation surgery (90 versus 47%) [33] raising the prospect that this might add value in decision making about PET as an option. The recent POETIC study undertook whole exome sequencing of ER positive breast cancers and found that a high mutational load and the TP53 mutation were both associated with poor antioestrogen response [34]. Other tissue biomarkers including a 4-gene signature [35] and apoptosis markers are also potentially valuable.

Tissue re-biopsy after treatment has started is an effective way to predict treatment response and the best-known marker for PET is Ki67, a marker of proliferation. If this falls at 2 weeks then the tumour is more likely to have a good sustained response [36]. The need for a further invasive biopsy in frail older women makes these methods less valuable.

Currently there is much interest in the use of ‘liquid biopsies’ to assess circulating tumour cells or cell free tumour DNA [37, 38]. Again, there has been no application of these technologies in the older age group PET setting but they have potential to avoid re biopsy in the event of progression to allow a more tailored approach to change of management with reduced morbidity. These technologies are being evaluated in managing advanced breast cancer progression where decisions about multiple lines of complex chemotherapy and targeted biologicals may be guided by such tools.

### 5.3.2 Antioestrogen Drugs for Use in PET

As can be seen from Table 5.1 above, rates of response to antioestrogens are generally high, although complete response is not common. There is a trend for aromatase inhibitors to yield higher clinical benefit rates than tamoxifen which is in

keeping with published studies of use of AIs compared to tamoxifen in other clinical settings such as adjuvant [39], and neoadjuvant [40, 41]. Therefore unless specifically contraindicated, AIs should be used in preference to tamoxifen as first line endocrine therapy for PET.

#### 5.3.2.1 Tamoxifen Versus Aromatase Inhibitors

Comparison of letrozole with tamoxifen in the neo-adjuvant setting in 337 postmenopausal women demonstrated a significantly higher clinical response rate in the letrozole group (55% versus 36%, $P < 0.001$) at follow-up of 4 months [40]. Of interest was the fact that letrozole was superior to tamoxifen regardless of the level of ER positivity, even inducing response in only weakly ER positive tumours, where tamoxifen was ineffective.

Another neo-adjuvant Letrozole study demonstrated that Letrozole was effective in reducing the size of large primary cancers considered unsuitable for breast conserving surgery. This study found that whilst in most women the best response had been achieved by 4 months of therapy, further benefit was seen at up to 8 months with letrozole which was the maximum period of neo-adjuvant therapy [42]. They found a 62% reduction in tumour volume at 4 months and 70% at 8 months.

Similarly, anastrozole is superior to tamoxifen in the neo-adjuvant setting and has been studied in 2 trials: IMPACT and PROACT. In the IMPACT study (IMmediate Pre-operative Arimidex, Tamoxifen or Combined with Tamoxifen), 330 women with a median age of over 70, found a significantly higher rate of breast conservation with anastrozole compared to tamoxifen when used for only 3 months prior to surgery (46 versus 22%) [43].

The PROACT study compared 12 weeks of pre-operative anastrozole or tamoxifen (PRe-Operative Arimidex Compared to Tamoxifen, [44]), in women with large operable or potentially operable breast cancer. Anastrozole resulted in increased rates of breast conservation versus tamoxifen (43 versus 31%, $P < 0.04$), and numerically superior clinical response rates (36 versus 26%).

Exemestane has also been used in the neoadjuvant setting and has a similar efficacy to anastrozole [45].

#### 5.3.2.2 Fulvestrant

Fulvestrant is a pure ER receptor antagonist which is licenced for use in the advanced breast cancer setting where it has been shown to have superior efficacy to anastrozole (if used at the correct 500 mg dose) [46, 47]. It has not been studied in the PET setting and is rarely used clinically due to costs and the fact that it must be given by injection.

#### 5.3.2.3 Agents for the Future

There has been huge development in targeted biological agents for use in breast cancer and although none of these are being trialled in the PET setting there may be roles for them in the future in second or third line therapy where surgery is not an option. Drugs such as bisphosphonates may have a role as an adjunct to PET both to reduce

the osteopenic side effects of AIs but also, recent evidence suggests they may have a small survival impact in women with post-menopausal breast cancer [48].

Other agents with high efficacy rates in ER positive breast cancer are the CD4/6 kinase inhibitors palbociclib and ribociclib which are co prescribed with aromatase inhibitors and enhance response rates significantly in the metastatic setting [49] and show high efficacy rates in the neoadjuvant setting [50]. There is little experience with these agents in older patients however and none in the PET setting.

## 5.4 Patient Selection for Primary Endocrine Therapy

Several studies have explored the selection criteria for PET in the older breast cancer population. In the UK, 45% of PET patients were high risk for general anaesthesia due to co-morbidity; in 8.5% of cases they were offered PET on the basis of extreme old age (over 85 years); in 10.6%, they were significantly cognitively impaired and in 36% of cases they were offered a choice of PET or surgery and chose PET [7]. Another UK study that examined the use of PET quoted a figure of 32% for patients being selected due to unfitness for surgery [25]. Functional status and chronological age are more likely to predict the use of PET than co-morbidity [8]. Similar figures were quoted by Hooper and colleagues [51] in their Irish cohort, with 62% offered PET based on the presence of significant co-morbidity (including dementia), 14% based on age and 11% based on patient preference. In the Netherlands Hamaker and colleagues found that co-morbidity accounted for only 6% of the decision to omit surgery and overall health status for only 5% in their study [52] with 32% being due to patient request. This is in contrast with results from the UK, where Rai and colleagues [53] found only 4% of patients treated without early surgery were due to patient choice and Lavelle and colleagues [54] who stated that lower rates of surgery were unlikely to be due to patients actively opting out of surgery.

The assessment of older patients for surgical fitness is complex and time consuming and detailed assessment is out-with the scope of many breast units both in terms of time and geriatric expertise availability. One study [55] reported on the use of comprehensive geriatric assessment (CGA) in a joint clinic with geriatrician input into the decision making process for older women. They found that CGA permitted relatively accurate prediction of 3-year survival and that good survival scores were indicative of benefit from surgery.

Stratified analysis of outcomes from surgery or PET do show that surgical benefit is more likely to be seen in fitter, younger women as shown in the study by Ward and colleagues. This examined UK registry data and stratified by age subgroup and comorbidity rates and found that as both age and comorbidity levels rise, differential breast cancer specific survival narrows significantly (Fig. 5.4) [56].

Age has a marked impact on rates of surgery. The recent National Audit of Breast Cancer in the Older Patient (NABCOP) UK National audit shows clearly that rates of surgery decline markedly with age and this is consistent with several published studies that have identified a reduction in surgery rates with increasing age for older patients with operable breast cancer [57–59]. Life-expectancy is considered

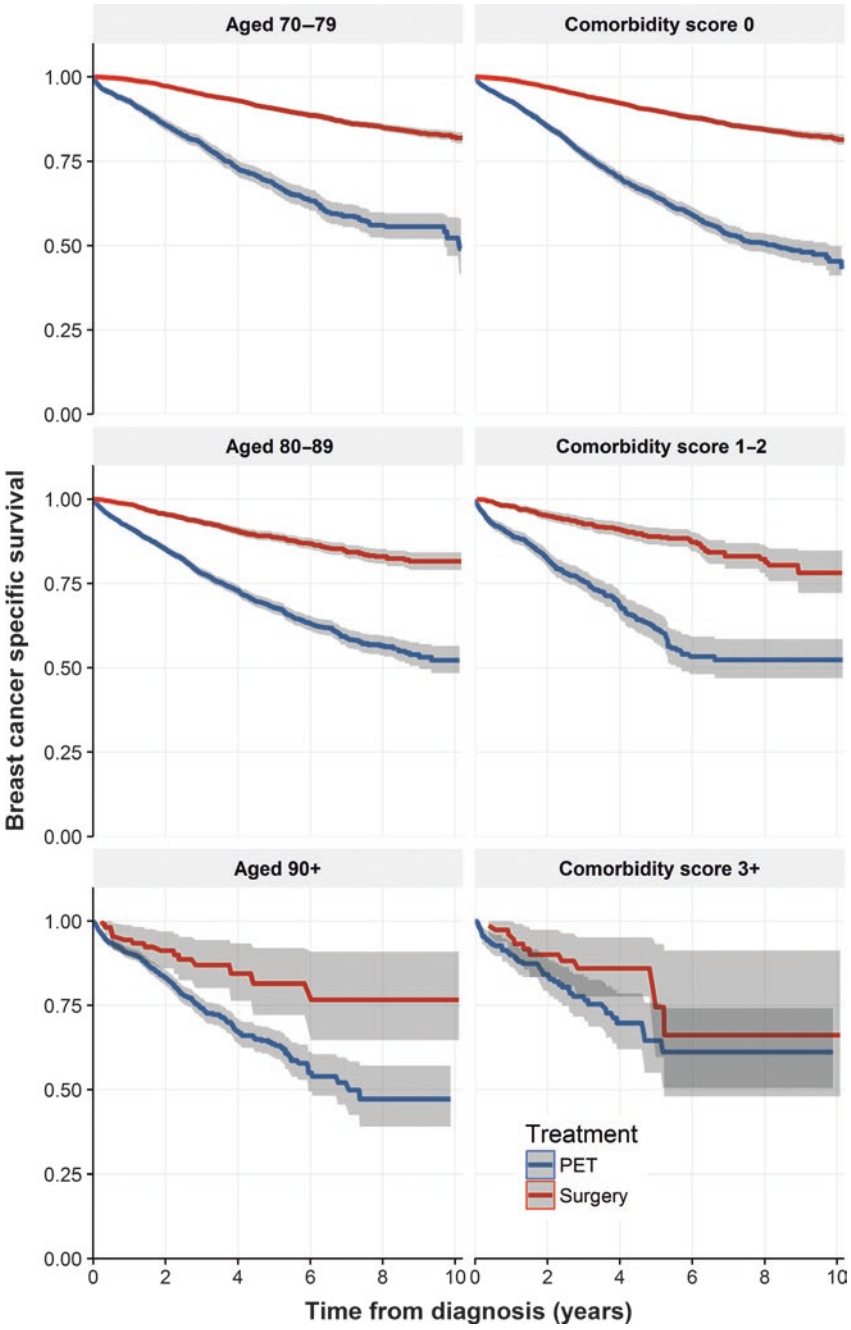


**Fig. 5.4** Breast cancer specific survival (BCSS) by age group (left) and by comorbidity score (right) for surgery and PET treatment of UK cancer registry data (2002–2012). These curves demonstrate that BCSS remains inferior for patients receiving PET despite older age or increasing numbers of co-morbidities. (Reproduced with permission from [56])

relatively important in how clinicians determine treatment options [60], and chronological age is often used by clinicians as a surrogate marker of life expectancy alongside other factors, such as comorbidity and frailty, 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 [17].

Several UK based observational studies have shown a clear association between use of surgery and the number of comorbidities. Lavelle and colleagues [61] in a registry cohort of over 65 s, found rates of surgery of 73, 66 and 49% according to comorbidity scores of 0, 1 or >2.

Some specific comorbidities have been examined for their impact on breast cancer treatment selection and outcomes. Dementia is the most notable of these.

Significant cognitive impairment affects up to 10% of people over the age of 65, and is more prevalent in women where the rate increases to 20% for women aged between 85 and 89 years of age [62]. As a result, dementia is a common comorbidity in older breast cancer patients and is associated with a significant reduction in life expectancy and is a leading cause of death for women in the UK [63]. Dementia may preclude surgery under local anaesthesia and cognitive and functional ability may worsen following general anaesthesia [64], so for patients with ER+ breast cancer and dementia, PET may be an effective alternative. In fact there are studies that have examined the use of PET in small cohorts of elderly patients which have suggested that the presence of dementia may have been a contributing factor in treatment decision making in some patients [30, 51, 65–67]. Studies from the USA have shown that women with dementia are less likely to receive standard treatment such as surgery for their breast cancer [68, 69]. However, a survey of clinicians showed that opinion was divided regarding the best treatment approach in elderly breast cancer patients with dementia. There are currently no UK guidelines for the treatment of operable breast cancer in this complex group of patients, which may reflect this lack of consensus

### 5.4.1 Psychological Response and Quality of Life

There has been little formal study of the quality of life impact of surgery versus PET in this age group. Only one of the historic randomised trials compared QoL outcomes between women having surgery or PET using the general health questionnaire, which is a generic tool and not very sensitive for detecting the impacts of breast cancer treatment [70]. Whilst this study showed a small difference in QoL when measured during early follow up, by 2 years, any differences had disappeared. This is somewhat surprising considering the proven negative impacts of breast surgery on quality of life. One would expect that breast cancer surgery would have a detrimental effect on at least short term QoL as has been shown in a number of studies where breast cancer specific instruments have been used.

Breast cancer surgery has detrimental effects on QoL, with adverse effects at 1 month post-operatively (fatigue, loss of function and pain). These effects may persist for a long time, with up to 45% still complaining of fatigue and 15% still struggling with household chores, at 12 months [71]. In addition chronic wound pain may

affect 75% of women following breast cancer surgery, regardless of type (50% mild, 25% moderate), which may impact on QoL. In 35% of breast cancer patients the pain is of neuropathic origin, and therefore relatively difficult to control [72].

In contrast for women on PET, there may be additional concerns about treatment failure or recurrence sometimes due to the continued presence of the palpable lump: fear of cancer progression or recurrence affects quality of life [73].

Lavelle and colleagues looked at a range of quality of life measures after breast cancer diagnosis and found that scores were worse in women who went on to have PET but did not assess QoL after treatment and deduced that this may have been a factor in treatment decision making [54]

A very small study comparing QoL in older women treated with or without surgery showed no significant differences at 6 weeks or 6 months between groups but was underpowered and therefore no valid conclusions could be drawn from this [74].

More recently the Age Gap study has undertaken a more rigorous approach to QoL impacts, using a range of validated QoL tools (the generic cancer EORTC QLQ C30, the breast specific EORTC BR23 and the elderly specific EORTC ELD14) at baseline and at intervals up to 2 years with adequate study power to detect differential responses. The results are complex to interpret as the study is a pragmatic observational study and therefore baseline characteristics vary between women having surgery and those having PET. When this variance is adjusted for using propensity score matching and variation in baseline QoL there is a significant disadvantage to surgery in many of the QoL domains in a matched cohort of frail older women, which persists in some domains out to 2 years [75]. As can be seen in the limited data reproduced below (Fig. 5.5), global QoL falls from 72 to 61 between pre-treatment baseline and 6 months in surgically treated women, compared to a fall of only 68 to 64 in the PET group ($P < 0.05$). Similarly, in the physical function domain there is a fall of 11 points compared to only

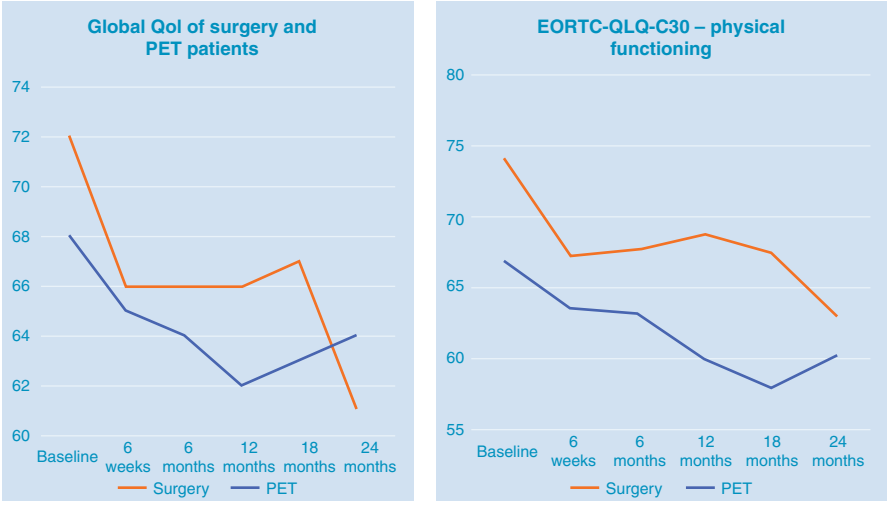


**Fig. 5.5** Quality of life outcomes from baseline to 2 years follow up of propsensity score matched cohorts of women treated with surgery (red) or PET (blue) [75]

a 7 point decrease in PET patients. In several other domains significant falls in QoL were seen for surgery to be greater than for PET and in no domain was surgery superior. This is not surprising due to the impacts of surgery (chronic pain, disfigurement, arm and shoulder symptoms) and the lack of resilience to the effect of anaesthesia in this group of frailer women.

The psychological impact of PET has been studied in older women using qualitative methodology and potential concerns about anxiety relating to the continued presence of the tumour are not realised as women felt reassured that they were able to feel the lump shrinking. In general many women who chose PET did so because of a wish to avoid surgery and anaesthesia, a wish to reduce the burden on their carers and family, a pragmatic sense of acceptance of their likely limited life expectancy and ability to tolerate such treatment [76]. Detailed interviews with women who had previously had PET or surgery in this older age group have shown that older women tolerate both therapies very well [76]. Women on PET are unconcerned by the persistence of a palpable lump in the breast. In fact, the reverse is true and most are reassured that they can feel the lump themselves and know that the endocrine therapy is still working. Older women find PET a simple and attractive option, despite awareness that the treatment may not control their disease indefinitely. They are concerned that there be as little disruption to their normal daily life as possible. Surgery mandates a hospital visit about which many older women have anxieties. Surgery for some older women will take the form of a mastectomy and for many, the loss of a breast is a source of distress. Many older women are concerned about the risks of surgery and anaesthesia. Of those women who do have surgery however, many find the experience tolerable.

### 5.4.2 Survival Outcomes

Whilst the historic randomised trials have not shown significant overall survival advantage to surgery on meta analysis (Fig. 5.1), subgroup analysis of a cohort of women between 70 and 75 did show improved survival [77]. Very long follow up has shown improved survival in some studies.

The RCTs referenced above do not represent modern real world practice as they recruited women of any level of fitness over age 70 and, in most cases, only frailer, older women are offered PET today. Observation data of UK practice and outcomes from cohort studies and registry analysis has confirmed the perception that breast cancer specific survival is superior in women having surgery, although stratification by age and fitness suggests that the oldest old and those with significant health issues derive no benefit (Fig. 5.4).

### 5.4.3 Patient Decision Making

Older women differ slightly in their desire for involvement in medical decision-making and tend to be slightly more passive in their approach. However this is not always the case and there is great variability in this. At present there are no bespoke,

age appropriate decision support tools for older women faced with this choice and most counselling is supported using booklets designed to support use of adjuvant antioesrogens and primary surgery with no resources to fully explain the nature of PET, the risks of potential benefits. A large UK study has recently developed a range of decision support tools specifically for this task, tailored to the informational needs and preferences of older women [78, 79]. These comprise a booklet and an online tool that can calculate survival rates at 2 and 5 years with either choice and which is responsive to age, fitness, frailty and disease biology. The output from this tool can be printed in a user-friendly format to be used in counselling older women. The tools are at present being evaluated in a cluster RCT nationally and will be published in 2019 [80].

### 5.4.4 Clinician Involvement

Clinicians vary in their attitudes to offering PET and the relative weights they place on patient and disease attributes when making these decisions. A recent survey of MDTs by the RCS as part of the National Audit of Breast Cancer in Older People (NABCOP) gave MDTs a set of patient scenarios and asked whether PET or surgery would be preferred. The results showed that whilst the majority of clinicians had similar views, some scenarios clearly divided opinion and in all scenarios there was a significant minority holding counter views, all of which shows the heterogeneity of opinion in this area. A survey of 244 UK healthcare professionals also demonstrated how opinions differ regarding the use of PET, especially in those patients with dementia. There was a general consensus that patient preference was the most important factor when considering treatment options, yet only around a quarter would offer it as a choice in patients with ER positive disease [60] .

A more rigorous example of scenario based evaluation of breast clinicians showed that decisions were significantly affected by age, dementia, frailty and fitness [16]. Again, whilst the majority of individuals selected treatment in accordance with current guidelines relating to the presence of significant comorbidity, in some scenarios, opinion was divided and age did appear to be an independent factor that was considered when making a treatment decision.

Hamaker and colleagues have also suggested that variation in treatment may reflect underlying clinician preference influencing communication of treatment options [52]. An interview study of older breast cancer patients demonstrated that the most influential factor affecting older women's breast cancer treatment decisions was the surgeon's recommendation [81].

## 5.5 Summary

Primary endocrine therapy for women with primary, operable breast cancer should be reserved for women with moderately or strongly ER positive tumours and who have a predicted life expectancy of less than 5 years (that is women of over 85 or

those over 75 with significant co-morbid disease). Close monitoring during the first year of therapy should aim to identify those who have a complete or partial response who may be predicted to have a long duration of local disease control. For those with static or progressive disease, early consideration should be given to surgery, either under local or general anaesthesia as these tumours are unlikely to have a long duration of disease control. For frailer women or those who refuse surgery on progression, second line endocrine therapy may be offered (switching between Tamoxifen and an AI or *vice versa*), although the duration of response may be less than with the primary agent used. Radiotherapy may also be a good second line option.

In terms of the choice of endocrine therapy, there is good evidence that aromatase inhibitors should be preferred unless specifically contraindicated, but bone density will need to be monitored and treated. In terms of which AI to use, the strongest evidence of efficacy relative to Tamoxifen is for Letrozole, but all AIs have been demonstrated to be effective in the short-term neo-adjuvant setting.

Older women who are thought suitable for a choice of PET or surgery should be offered a role in the decision making process. Both surgery and PET are generally well tolerated although QoL outcomes may be slightly worse with surgery, but the trade off is the slightly enhanced oncological outcomes with surgery. This trade off should be discussed with patients so they may set their own priorities.

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