An observational study investigating failure of primary endocrine therapy for operable breast cancer in the elderly

Robert Thomas, Rachel Rowell, Siobhan Crichton, Henry Cain

1. First and corresponding author:

Robert Thomas

Specialist Trainee General and Breast Surgery

Queen Elizabeth Hospital, Gateshead, UK. NE9 6SX

Email: roberthuwthomas@doctors.org.uk

(permanent address: 48 Larkspur Terrace, Jesmond, Newcastle Upon Tyne, UK NE2 2DU)

2. Second author

Rachel Rowell

Foundation Programme Doctor

Royal Victoria Infirmary, Queen Victoria Road, Newcastle Upon Tyne, UK NE1 4LP

Email: Rachel.rowell2@nuth.nhs.uk

3. Third author

Siobhan Crichton

Medical Statistician

Medical Research Council Clinical Trials Unit at University College London

Aviation House, 125 Kingsway, London WC2B 6NH

Email: Siobhan.Crichton@outlook.com

4. Fourth author

Henry Cain

Consulant Oncoplastic Breast Surgeon

Royal Victoria Infirmary, Queen Victoria Road, Newcastle Upon Tyne, UK NE1

4LP

Email: henry.cain@nuth.nhs.uk

Abstract

Background

Elderly patients are more likely to have oestrogen receptor positive cancers that can be treated without surgery with Primary Endocrine Therapy (PET). Few studies have sought to identify predictors of failure of PET and so the aim of this study was to evaluate treatment failures in elderly breast cancer patients treated with PET and to determine predictors of failure.

Methods

A retrospective observational study was performed on consecutive patients with ER positive early stage breast cancer treated with PET between 2005 and 2015 in the three breast units in the north east of England. The primary outcome measure was treatment failure and secondary outcome measure was disease progression.

Results

488 patients were included with mean follow up 31 months (SD 23). Overall, 206 patients were still alive with their disease controlled at the end of follow up, 219 had died with their disease controlled and 63 (12%) experienced treatment failure. Younger age [SHR 0.96 (95% CI 0.94 to 0.99) p 0.013], larger tumours [SHR 1.03 (1.01 to 1.06) p 0.015], grade 3 cancers [SHR 3.58 (1.93 to 6.63) p<0.001] and axillary lymph node metastases [SHR 1.93 (1.06 to 3.52) p 0.030] were all independent predictors of treatment failure. Disease progression was reported in 86 (17.6%) of patients.

Conclusions

This is the largest retrospective series evaluating PET treatment failure. Clear predictors of failure have been identified, which can be used to facilitate treatment decision-making. These results support previous analyses, further validating our results.

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Keywords

Primary endocrine therapy; breast cancer; elderly

INTRODUCTION

Frailty and the burden of co-morbid disease increase with advancing age[1], as does the incidence of breast cancer[2]. Whilst surgery is the standard initial treatment of choice for early breast cancer[3], some elderly and frail patients with oestrogen receptor (ER) positive cancers who are considered too unfit for general anaesthesia, may be given primary endocrine therapy (PET)[4,5]. PET has been shown to be effective in treating breast cancer[6].

PET use has become widespread. In 2012 a UK-based questionnaire study reported that 93% of surgeons advocated the use of PET in early operable breast cancer in the elderly[7]. Whilst PET provides relatively good local control in the short term (2-3 years), it has been found to be inferior to surgery long-term. This was shown in a Cochrane meta-analysis that showed no difference in overall survival between PET and surgery, but an inferiority of PET in local disease control[8]. However, all but one study included were unselected for oestrogen receptor (ER) status, and all used Tamoxifen which has now largely been superseded by Aromatase inhibitors (AIs)[9].

The International Society of Geriatric Oncology (SIOG) advise that PET may be considered in patients with a short life expectancy (<2 years) or unfit for surgery[10]. Frequently, clinician's decision making in allocating PET is subjective, made in a busy time-pressured outpatient clinic, with little objectivity. NHS time- targets may also influence clinician's decision making[11], as formal anaesthetic or geriatric opinions can take time.

Treatment failure on PET is potentially catastrophic for the patient. As such, patient selection is key. Difficulties in patient selection are compounded by an increasing life expectancy, with patients with multiple co-morbidities able to live longer due to improvements in geriatric and medical care[12-14]. Few studies have directly sought to analyse failure of PET. The aim of this study was to determine the failure rate of PET in the North East of England, and to identify predictors of failure.

METHODS

An observational study was performed on patients with ER positive early breast cancer treated with PET between January 2005 and December 2015. Data collection was performed retrospectively and subjects were identified from the three North East of England breast-screening units. Local breast cancer multi-disciplinary team databases were used to select patients. Patients were excluded if they had inoperable or metastatic disease at presentation, or if endocrine therapy was given as neo-adjuvant treatment to downstage the tumour prior to surgery.

Tumour characteristics

Pathological information was based on needle-core biopsies on first presentation. Strength of ER status was determined by the histochemical 'quickscore' (value out of eight)[15]. HER-2 positivity was defined by immunohistochemistry or fluorescent in-situ hybridization (FISH) in borderline cases[16]. The grade of the tumour was catergorised 1-3 by the modified Scarf-

Bloom-Richardson (SBR) criteria[17]. Lymph node involvement was recorded either from histology or cytology, and in some cases based purely on ultrasound appearances if a tissue-sample was not acquired. Tumour size was based on the maximum dimensions from ultrasound.

Treatment decisions and patient characteristics

Patients were seen for diagnosis and treatment planning in the outpatient clinic, with support from the local Multidisciplinary team (MDT). Case notes and outpatient clinic letters were reviewed to determine the first choice of endocrine agent. Data on patient co-morbid disease, cognition and social circumstances was also collected. Consultation by geriatricians or anaesthetists was recorded. The use of predictive indexes which facilitate decision making were recorded, as was any additional information on other surgeries unrelated to their breast cancer following diagnosis.

Follow up

Length of follow up was determined by case note review. The date of diagnosis was taken from when the diagnosing histology was made available. Patients were ultimately followed up until they died, or were still under follow up at the censor point (December 2015). Cause of death was either determined from the case notes or from the patient's general practitioner.

Outcome variables

The primary outcome measure was treatment failure. This was defined as patients either dying with uncontrolled local disease; patients dying of

metastatic breast cancer (where there was only local disease on presentation), or patients requiring surgery or radiotherapy to control local progression. Time to failure was recorded either from diagnosis to death, or diagnosis to surgery or radiotherapy. Treatment was considered a success if the patient died of causes unrelated to their breast cancer and their disease was under control at that point, or if they were still alive at the time of censoring with their disease controlled.

The secondary outcome measure was disease progression. This was defined as an increase in size of tumour whilst on PET. Time to progression was recorded from diagnosis to when the tumour clinically or radiologically increased in size.

Statistical analysis

Patients still alive without treatment failure were censored at end of follow-up at end of December 2015. Characteristics in the three groups (treatment failures, patient who died with controlled disease and patients still alive with controlled disease) were compared using the Kruskal Wallis test, Chi-square test or Fisher's exact test, as appropriate. Where patients had bilateral disease, tumour size and characteristics were summarised using data from the largest or most advanced tumour.

The cumulative risk of death with controlled disease and risk of treatment failure was calculated with the alternate outcome treated as a competing risk.

Competing risks regression models were used to identify factors associated with dying with controlled disease and with treatment failure. Results are presented as sub-hazard ratios (SHR) with 95% confidence intervals (CI).

Analysis was carried out using STATA 14IC.

RESULTS

Data were included from 488 patients who were followed for a total of 1271 person years. Among all patients the mean follow up was 31.3 (standard deviation = 23.0) months with a median of 28 months (Interquartile range = 5 to 41). Among 232 patients who died mean follow up was 27.4 (24.0) months and median 21 (10 to 36 months). The remaining 255 patients were alive at the end of December 2015 by which time they had provided a mean follow up of 35.5 (21.1) months and median of 32 (21 to 45) months. 465 (95.2%) patients were started on Letrozole as their initial therapy, Tamoxifen in 18 (3.7%) and the remaining 5 (1.1%) either Anastrazole or Exemestane.

Patient characteritistics

Characteristics of included patients are summarised in table 1. Overall, 206 patients were still alive with their disease controlled at the end of follow up, 219 had died with their disease controlled and 63 experienced treatment failure. Patients who died with their disease controlled were older at diagnosis ($p=0.014$) and had more comorbidities ($p=0.010$) than other patients. Median tumour size at diagnosis was 30mm in those who failed treatment, compared to 25mm in others ($p=0.038$). Tumours in patients who failed treatment were also more likely to be TPM grade 3 ($p<0.001$) and almost half of the patients had lymph node involvement compared to <20% in patients without treatment failure ($p<0.001$).

Risk of treatment failure

The cumulative risks of death with disease controlled and of treatment failure are summarised in Table 2 and Figure 1. By 12 months 15.6% (12.5 to 19.0) patients had died without treatment failure, rising to 51.5% (45.8 to 56.9) at 60 months and 65.1% (57.8 to 71.4). By the 96 months 20.8% (15.8 to 26.2) of patients had experienced a treatment failure.

Predictors of treatment outcome

The associations between patient and disease characteristics and both death with disease control and hazard of treatment failure were explored with the results summarised in table 3. Increasing age, more comorbidities, impaired mobility, cognitive impairment and nursing home residency were all associated with dying with disease controlled. Patients who were older, with more comorbidities and less independent were more likely to die with their disease controlled.

On the other hand, tumour size, TPM grade, axilla involvement and vascular involvement were the only factors associated with treatment failure. Patients with large and more advanced disease are more likely to experience treatment failure.

Next, multivariate regression analysis was used to identify all independent predictors of dying with disease controlled and of treatment failure with the results summarised in table 4. Increasing age and more comorbidities were both independent predictors of dying with disease controlled. The likelihood of dying with controlled disease increased by 2% for every year increase in age (SHR=1.02, 1.00 to 1.04). Younger age (SHR=0.96, 0.94 to 0.99), increasing TPM

grade (SHR=3.58, 1,93 to 6.63) and axilla involvement were also associated with treatment failure, with patients with axilla involvement almost twice as likely to experience treatment failure (SHR=1.93, 1.06 to 3.52).

Details of treatment failures are summarised in table 5. Of the 63 patients who experienced failure, 32 (50.8%) died with uncontrolled disease and 22 (34,9%) from breast cancer. The median time to first failure was 28 (14 to 41) months.

Disease progression was reported in 86 (17.6%) of patients. Of those 66 (80.5%) continued on PET, usually with a change of agent. Treatment failure was observed in 51 (59.5%) who had progressed, 18 (20.9%) had died without failure and the remaining 17 (19.8%) were still alive without failure at end of December 2015.

Treatment planning

270 (55.3%) patients were offered surgery in the first instance.

46 (9.4%) patients were referred for an anaesthetic assessment as part of their treatment planning. 5 (1%) patients had a geriatric assessment. 17 (3.4%) had a documented frailty or risk score performed by the surgeon. 14 patients had surgery following their diagnosis on unrelated problems requiring general anaesthesia, of which 3 were for hip or knee arthroplasty.

DISCUSSION

Advanced age and a higher burden of co-morbid disease are associated with dying with controlled disease. Younger patients, who tend to live longer, are more likely to experience treatment failure. Younger patients with higher histological grade, larger tumours and axillary lymph node metastases are most at risk of treatment failure.

This observational study provides the largest retrospective patient series in the literature investigating treatment failure of PET in elderly women. Previous failure rates of PET that have been published range from 12% to 84%[18-32]. Many of these included patients unselected for ER status however, and used Tamoxifen as the primary treatment. Letrozole was the predominant drug of choice in over 95% of our cohort. Whilst the superiority of Aromatase Inhibitors (AIs) has been shown in the adjuvant[33], neo-adjuvant[34] and palliative settings[35] in post-menopausal women, no randomised trial exists for comparison for use as a primary endocrine agent. However, with our comparatively low rate of treatment failure (12.9%), this suggests an advantage of Letrozole over Tamoxifen for use in PET. Our low rates of failure also suggest good clinical acumen, despite the lack of additional specialist input.

Randomised trials comparing surgery with PET identified the superiority of surgery in controlling local disease long-term, which suggested that PET could be given to good effect in the short-term, but those living longer were more at risk of disease progression. However, few trials have sought to determine other factors associated with PET failure. Most recently, Layfield et al [36] reported

that high-grade disease and axillary lymph node involvement independently predicted early failure. Tumour size has also been found to be an independent predictor[23], although this was in a cohort unselected for ER status. Our findings, in a larger cohort, not only validate these previous results but also found that histological evidence of vascular invasion (SHR 2.48 CI [1.15 to 5.34] p=0.020) was significantly associated with treatment failure in univariable regression analysis. An early study associated HER-2 positivity with treatment failure[37], however our results failed to show this, likely due to the low numbers in our cohort with positive HER-2 status.

The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA)[10] recommend that PET should only be offered to patients with a "short estimated life expectancy (less than 2 to 3 years), who are considered unfit for surgery or who refuse surgery". The mean time to failure in our cohort was about 30 months, with the mean time to requiring radiotherapy and surgery 26.5 and 29.7 months respectively. On one hand, this would support such a time frame. However, the probability of a patient at three years of dying of a non-breast related cause with controlled local disease is 39%, with a 10% failure probability. This means that approximately half of patients would still be alive with controlled local disease at this point. Then, looking further ahead at five years, just fewer than 35% of patients would be predicted to still be alive with disease control. One could therefore argue that PET does have a role longer term contrary to current guidance. Ultimately in clinical practice patient choice plays a crucial role.

As part of the Bridging the Age Gap in Breast Cancer Trial[38], Morgan et al reported that increasing age, higher levels of comorbidity, large tumour size and dependence in one or more ADL categories were strongly associated with non-surgical treatment. We found that those older, more co-morbid patients were more likely to die of non-breast cancer related causes with their disease controlled and thus have successful treatment with PET. Interestingly larger tumour size independently predicted treatment failure in our cohort and so taking into consideration initial results by Morgan et al, if a patient is fit enough for surgery then they should be encouraged to have it.

Despite evidence that clinical judgment alone is an inaccurate measure of life expectancy[39,40], we could not demonstrate a difference in failure between those who had additional non-surgical clinical input and those whose decisions were made by the surgeon alone. This is because few patients had allied-health reviews. The low uptake of geriatric and anaesthetic involvement may reflect local service challenges, and highlight that decision making for PET is largely subjective. SIOG advises geriatric involvement in all elderly cancer treatment decision-making processes, but none of the local units involved in this study within the time frame for recruitment had routine access to specialist surgical and oncological liason geriatricians. This may help explain why 14 patients had surgery for non-breast related problems following their breast cancer diagnosis, including 3 joint replacement operations.

Morgan et al[38] acknowledged the difficulty in recruitment in trials involving the elderly[41]. Conducting a retrospective observational study such as this

avoids such issues. However, there are limitations. The majority of the information gained was reliant on case records, in particular treatment decisions, documentation of co-morbidities, living arrangements and mobility. There was a large degree of heterogeneity in how comprehensive clinic letters were. To account for this, nursing notes, routinely filed in the case records were also examined. Surveillance of tumours was also variable. Some patients would purely have clinical follow up where clinical examination would assess for disease control, whereas others would use mammography and ultrasound. Much of these problems are the result of a retrospective study design, and involving breast units from three independent NHS trusts. There is a positive however of a multi-institution study as it reflects wider practice and natural variations between units. This in turn makes the results more generalisable to other breast units.

This series has identified key factors associated with treatment failure on PET. Younger patients, with larger high-grade tumours and axillary node metastases would benefit from surgery over primary endocrine therapy. Patients with limited life expectancy, can be treated with PET as it likely they will die from non-breast cancer related causes. Treatment decision making in elderly patients in routine clinical practice is a challenge, particularly as not all patients fall into two distinct groups as described above. There is evidence from this series that some patients living beyond three years can maintain disease control longer-term, and as such adds to the difficulty in accurately advising patients as to the most appropriate treatment. Surgery has been shown to be safe with regional anaesthesia[42], allowing increasingly frail patients greater access to surgery,

and as such should be the standard of care for operable breast cancer. PET with AIs in post-menopausal women may be a viable long-term alternative in the right circumstance and in the absence of failure risk factors. A specific prognostic index to identify the likelihood of treatment failure would give more objectivity in treatment planning, allowing the clinician to counsel the patient appropriately. However, no such model is yet widely available.

Tables and Figures

Table 1. Patient and disease characteristics by outcome

	All	Alive with disease controlled	Died with disease controlled	Failed treatment	p-value
Total	488	206	219	63	
Age at diagnosis, median (IQR)	83 (78.5 to 88)	82.5 (78 to 87)	85 (79 to 90)	83 (77 to 87)	0.014
Tumour size, median (IQR), (missing: n=6)	25 (20 to 35)	25 (18 to 35)	25 (20 to 34.5)	30 (20 to 45)	0.038
Bilateral disease, n (%)	22 (4.5)	12 (5.8)	8 (3.7)	2 (3.2)	0.481
HER2 Pos, n (%) (missing: n=83)	32 (7.9)	14 (8.1)	11 (6.1)	7 (13.5	0.218
TPM grade, n(%) (missing: n=19)					<0.001
1	49 (10.5)	25 (12.8)	21 (9.9)	3 (4.9)	
2	361 (77.0)	153 (78.5)	169 (79.3)	39 (63.9)	
3	59 (12.6)	17 (8.7)	23 (10.8)	19 (31.2)	
Strength ER positivity, n(%) (missing: n=5)					0.001
Weak (3-4)	5 (1.0)	1(0.5)	3(1.4)	1(1.6)	
Moderate (5-6)	12 (2.5)	1(0.5)	5(2.3)	6(9.5)	
Strong (7-8)	466(95.5)	202(98.0)	209(95.4)	55(87.3)	
Avilla involvement, n(%) (missing: n=3)	114 (23.5)	38 (18.6)	45 (20.6)	31 (49.2)	<0.001
Vascular invasion, n(%) (missing: n=16)	32 (6.8)	10 (5.1)	14 (6.5)	8 (13.6)	0.072
Histological subtype (missing: n=11)					0.556
IDC	375 (78.6)	159 (79.5)	166(77.2)	50 (80.7)	
ILC	70 (14.7)	30 (15.0)	30 (14.0)	10 (16.1)	
Other	32(6.7)	11 (5.5)	19 (8.8)	2(3.2)	
Prev unrelated Breast cancer, n (%) (missing: n=5)	31 (6.4)	11 (5.5)	17 (7.8)	3 (4.8)	0.634
Co-morbidities[a], n(%) (missing: n=5)	1 (1 to 2)	1 (0 to 2)	2 (1 to 2)	1 (0 to 2)	0.010
0	120 (24.6)	56 (27.2)	43 (19.6)	21 (33.3)	0.058
1 to 2	276 (56.6)	118 (57.3)	125 (57.1)	33 (52.4)	
3 or more	92 (18.9)	32 (15.5)	51 (23.3)	9 (14.3)	
Impaired mobility[b], n (%) (missing: n=6)	350 (71.7)	133 (64.6)	173 (79.0)	44 (69.8)	0.004
Cognitive impairment, n (%) (missing: n=3)	134 (27.6)	48 (23.7)	74 (33.8)	12 (19.1)	0.019
Carers at home, n (%) (missing: n=3)	129 (26.6)	42 (20.7)	67 (30.6)	20 (31.8)	0.039
Nursing home resident, n (%) (missing: n=3)	136 (28.0)	45 (22.2)	78 (35.6)	13 (20.6)	0.004

[a]Calculated as number of comorbidities from the following list: IHD, cardiac failure, stroke/neurological disease, significant pulmonary disease and diabetes

[b]Defined as using a walking aid or wheelchair

Figure 1: Probability of death with controlled disease and of treatment failure.

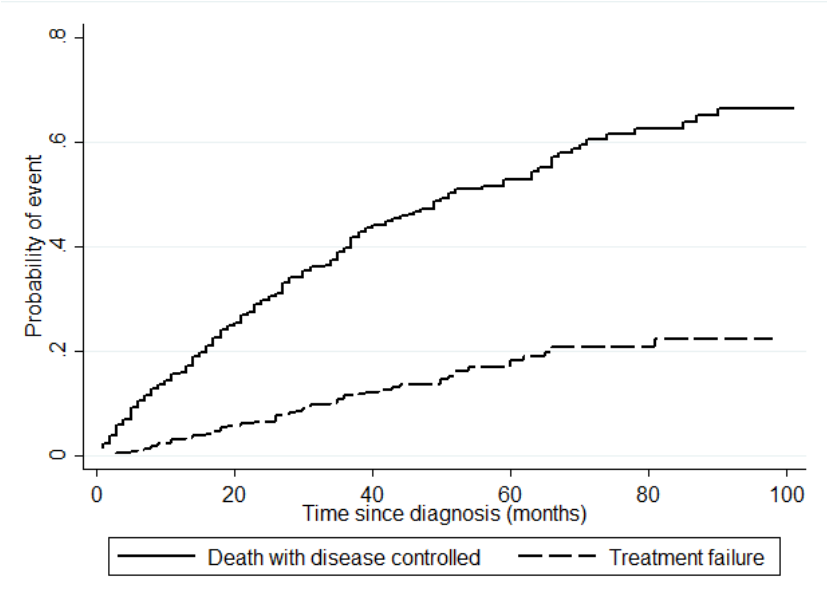

Table 2: Probability of death with controlled disease and of treatment failure.

Time	Cumulative percentage dying with disease controlled, % (95% CI)	Cumulative percentage with treatment failure, % (95% CI)
12 months	15.6 (12.5 to 19.0)	2.5 (1.4 to 4.2)
24 months	29.0 (24.9 to 33.2)	6.2 (4.2 to 8.6)
36 months	39.0 (34.3 to 43.8)	10.8 (8.0 to 14.1)
48 months	46.7 (40.5 to 50.8)	13.1 (9.8 to 16.8)
60 months	51.5 (45.8 to 56.9)	16.2 (12.4 to 20.7)
72 months	59.5 (53.0 to 65.5)	19.7 (15.1 to 24.8)
84 months	61.5 (54.7 to 67.5)	20.8 (15.8 to 26.2)
96 months	65.1 (57.8 to 71.4)	20.8 (15.8 to 26.2)

Table 3: Results of univariable competing risks regression analysis

	Event = Death with disease controlled			Event =Treatment failure		
	SHR	95% CI	p-value	SHR	95% CI	p-value
Age	1.02	1.01 to 1.04	0.010	0.98	0.97 to 1.00	0.076
Tumour size	1.00	0.99 to 1.01	0.394	1.03	1.02 to 1.05	<0.001
Bilateral disease	0.79	0.40 to 1.57	0.497	0.70	0.18 to 2.69	0.606
HER2 Pos	0.84	0.43 to 1.66	0.624	2.22	1.01 to 4.85	0.047
TPM grade	0.95	0.70 to 1.29	0.754	3.37	1.96 to 5.67	<0.001
Axilla involvement	0.81	0.58 to 1.13	0.216	3.69	2.27 to 6.00	<0.001
Vascular involvement	0.94	0.56 to 1.56	0.806	2.48	1.15 to 5.34	0.020
Strength ER positivity	0.91	0.76 to1.09	0.309	0.75	0.56 to 1.01	0.059

ILC	1.03	0.69 to 1.54	0.885	1,01	0.57 to 2.13	0.781
Other histological subtype	1.35	0.87 to 2.10	0181	0.41	0.10 to 1.60	0.199
Prev unrelated Breast cancer	1.08	0.71 to 1.66	0.715	0.63	0.20 to 2.00	0.429
Co-morbidities*						
0	1		0.015	1		0.154
1 to 2	1.32	0.93 to 1.86		0.65	0.38 to 1.11	
3 or more	1.80	1.21 to 2.70		0.52	0.24 to 1.11	
Impaired mobility	1.48	1.07 to 2.03	0.017	0.80	0.47 to 1.37	0.421
Cognitive impairment	1.52	1.16 to 1.99	0.002	0.59	0.32 to 1.12	0.106
Carers at home	1.21	0.91 to 1.60	0.187	1.25	0.74 to 2.11	0.400
Nursing home resident	1.63	1.24 to 2.15	<0.001	0.61	0.34 to 1.12	0.114

*Calculated as number of comorbidities from the following list: IHD, cardiac failure, stroke/neurological disease, significant pulmonary disease and diabetes.

Table 4: Factors associated with dying with disease control and treatment failure identified using competing risks regression with backwards selection.

	Event = Death with disease controlled			Event =Treatment failure		
	SHR	95% CI	p-value	SHR	95% CI	p-value
Age	1.03	1.01 t0 1.05	0.003	0.96	0.94 to 0.98	0.001
Tumour size				1.03	1.00 to 1.05	0.025
TPM grade				3.52	1.90 to 6.50	<0.001
Axilla involvement				2.01	1.09 to 3.73	0.026
Co-morbidities*						
0	1		0.009			
1 to 2	1.27	0.89 to 1.80				
3 or more	1.95	1.27 to 3.00				
Impaired mobility	1.31	0.95 to 1.83	0.102			

*Calculated as number of comorbidities from the following list: IHD, cardiac failure, stroke/neurological disease, significant pulmonary disease and diabetes.

Table 5: Summary of type and time to treatment failure.

	N(%)	Time to event, Mean (sd) Median (IQR)
Total failures/ time to first failure	63	30.3 (20.2) 28 (14 to 41)
Required radiotherapy	18 (28.6)	26.5 (19.1)

		20.5 (13 to 34)
Required surgery	26 (41.3)	29.7 (20.5) 25.5 (10 to 51)
Died with uncontrolled disease	32 (50.8)	37.3 (23.0) 33 (22 to 44)
Died of breast cancer	22 (34.9)	44.0 (22.3) 35 (30 to 51)

Declaration of Interests statement

HC is on the Clinical Advisory board for Roche Products Limited and received Honorariums and travel expenses; no other relationships or activities exist for all other authors that could appear to have influenced the submitted work.

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Authorship and Contributorship

RT and HC were responsible for the study concepts and design. Data acquisition was performed by RT and RR. Data and statistical analysis was performed by SC. Manuscript preparation, editing and review was performed by RT, RR, SC and HC.

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Ethical approval

No ethical approval was required for this retrospective study.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 6	An observational study investigating failure of primary endocrine therapy for operable breast cancer in the elderly
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6	A retrospective observational study was performed on consecutive patients with ER positive early stage breast cancer treated with PET between 2005 and 2015 in the three breast units in the north east of England. The primary outcome measure was treatment failure and secondary outcome measure was disease progression. 488 patients were included with mean follow up 31 months (SD 23). Overall, 206 patients were still alive with their disease controlled at the end of follow up, 219 had died with their disease controlled and 63 (12%) experienced treatment failure. Younger age [SHR 0.96 (95% CI 0.94 to 0.99) p 0.013], larger tumours [SHR 1.03 (1.01 to 1.06) p 0.015], grade 3 cancers [SHR 3.58 (1.93 to 6.63) p<0.001] and axillary lymph node metastases [SHR 1.93 (1.06 to 3.52) p 0.030] were all independent predictors of treatment failure. Disease progression was reported in 86 (17.6%) of patients.
Introduction				
Backgroun d/rationale	2	Explain the scientific background and rationale for the investigation being reported	8,9	Frailty and the burden of co-morbid disease increase with advancing age[1], as does the incidence of breast cancer[2]. Whilst surgery is the standard initial treatment of choice for early breast cancer[3], some elderly and frail patients with oestrogen receptor (ER) positive cancers who are considered too unfit for general anaesthesia, may be given primary endocrine therapy (PET)[4,5]. PET has been shown to be effective in treating breast cancer[6]. PET use has become widespread. In 2012 a UK-based questionnaire study reported that 93% of surgeons advocated the use of PET in early operable breast cancer in the elderly[7]. Whilst PET provides relatively good local control in the short term (2-3 years), it has been found to be inferior to surgery long-term. This was shown in a Cochrane meta-analysis that showed no difference in overall survival between PET and surgery, but an inferiority of PET in local disease control[8]. However, all but one study included were unselected for oestrogen receptor (ER) status, and all used Tamoxifen which has now largely been superseded by Aromatase inhibitors (AIs)[9]. The International Society of Geriatric Oncology (SIOG) advise that PET may be considered in patients with a short life expectancy (<2 years) or unfit for surgery[10]. Frequently, clinician's decision making in

				allocating PET is subjective, made in a busy time-pressured outpatient clinic, with little objectivity. NHS time- targets may also influence clinician's decision making[11], as formal anaesthetic or geriatric opinions can take time. Treatment failure on PET is potentially catastrophic for the patient. As such, patient selection is key. Difficulties in patient selection are compounded by an increasing life expectancy, with patients with multiple co-morbidities able to live longer due to improvements in geriatric and medical care[12-14].
Objectives	3	State specific objectives, including any prespecified hypotheses	9	Few studies have directly sought to analyse failure of PET. The aim of this study was to determine the failure rate of PET in the North East of England, and to identify predictors of failure.
Methods				
Study design	4	Present key elements of study design early in the paper	9,10	An observational study was performed on patients with ER positive early breast cancer treated with PET between January 2005 and December 2015. Data collection was performed retrospectively and subjects were identified from the three North East of England breast-screening units. Local breast cancer multi-disciplinary team databases were used to select patients. Patients were excluded if they had inoperable or metastatic disease at presentation, or if endocrine therapy was given as neo-adjuvant treatment to downstage the tumour prior to surgery.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11	As above
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of	9	Length of follow up was determined by case note review. The date of diagnosis was taken from when the diagnosing histology was made available. Patients were ultimately followed up until they died, or were still under follow up at the censor point (December 2015). Cause of death was either determined from the case notes or from the patient's general practitioner.

		selection of participants		
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11	The primary outcome measure was treatment failure. This was defined as patients either dying with uncontrolled local disease; patients dying of metastatic breast cancer (where there was only local disease on presentation), or patients requiring surgery or radiotherapy to control local progression. Time to failure was recorded either from diagnosis to death, or diagnosis to surgery or radiotherapy. Treatment was considered a success if the patient died of causes unrelated to their breast cancer and their disease was under control at that point, or if they were still alive at the time of censoring with their disease controlled. The secondary outcome measure was disease progression. This was defined as an increase in size of tumour whilst on PET. Time to progression was recorded from diagnosis to when the tumour clinically or radiologically increased in size.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11	Data collection was performed retrospectively and subjects were identified from the three North East of England breast-screening units. Local breast cancer multi-disciplinary team databases were used to select patients. Patients were excluded if they had inoperable or metastatic disease at presentation, or if endocrine therapy was given as neo-adjuvant treatment to downstage the tumour prior to surgery. Tumour characteristics Pathological information was based on needle-core biopsies on first presentation. Strength of ER status was determined by the histochemical 'quickscore' (value out of eight)[15]. HER-2 positivity was defined by immunohistochemistry or fluorescent in-situ hybridization (FISH) in borderline cases[16]. The grade of the tumour was catergorised 1-3 by the modified Scarf-Bloom-Richardson (SBR) criteria[17]. Lymph node involvement was recorded either from histology or cytology, and in some cases based purely on ultrasound appearances if a tissue-sample was not acquired. Tumour size was based on the maximum dimensions from ultrasound. Treatment decisions and patient characteristics Patients were seen for diagnosis and treatment planning in the outpatient clinic, with support from the local Multidisciplinary team (MDT). Case notes and outpatient clinic letters were reviewed to determine the first choice of endocrine agent. Data on patient co-morbid disease, cognition and social circumstances was also collected. Consultation by geriatricians or anaesthetists was recorded. The use of predictive indexes which facilitate decision making were recorded, as was any additional information on other

			surgeries unrelated to their breast cancer following diagnosis.
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	9

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11	Patients still alive without treatment failure were censored at end of follow-up at end of December 2015. Characteristics in the three groups (treatment failures, patient who died with controlled disease and patients still alive with controlled disease) were compared using the Kruskal Wallis test, Chi-square test or Fisher's exact test, as appropriate. Where patients had bilateral disease, tumour size and characteristics were summarised using data from the largest or most advanced tumour. The cumulative risk of death with controlled disease and risk of treatment failure was calculated with the alternate outcome treated as a competing risk. Competing risks regression models were used to identify factors associated with dying with controlled disease and with treatment failure. Results are presented as sub-hazard ratios (SHR) with 95% confidence intervals (CI).
		(*b*) Describe any methods used to examine subgroups and interactions	11	As above
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12	
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study	13	See table 1

		participants (eg demographic, clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of participants with missing data for each variable of interest	13	As above
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12	Data were included from 488 patients who were followed for a total of 1271 person years. Among all patients the mean follow up was 31.3 (standard deviation = 23.0) months with a median of 28 months (Interquartile range = 5 to 41). Among 232 patients who died mean follow up was 27.4 (24.0) months and median 21 (10 to 36 months). The remaining 255 patients were alive at the end of December 2015 by which time they had provided a mean follow up of 35.5 (21.1) months and median of 32 (21 to 45) months.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-14	Overall, 206 patients were still alive with their disease controlled at the end of follow up, 219 had died with their disease controlled and 63 experienced treatment failure.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15	See tables 2-5 and Figure 1
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives	18	Advanced age and a higher burden of co-morbid disease are associated with dying with controlled disease. Younger patients, who tend to live longer, are more likely to experience treatment failure. Younger patients with higher histological grade, larger tumours and axillary lymph node metastases are most at risk of treatment failure.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21	However, there are limitations. The majority of the information gained was reliant on case records, in particular treatment decisions, documentation of co-morbidities, living arrangements and mobility. There was a large degree of heterogeneity in how comprehensive clinic letters were. To account for this, nursing notes, routinely filed in the case records were also examined. Surveillance of tumours was also variable. Some patients would purely have clinical follow up where clinical examination would assess for disease control, whereas others would use mammography and ultrasound. Much of these problems are the result of a retrospective study design, and involving breast units from three independent NHS trusts. There is a positive however of a multi-institution study as it reflects wider practice and natural variations between units. This in turn makes the results more generalisable to other breast units.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-22	This series has identified key factors associated with treatment failure on PET. Younger patients, with larger high-grade tumours and axillary node metastases would benefit from surgery over primary endocrine therapy. Patients with limited life expectancy, can be treated with PET as it likely they will die from non-breast cancer related causes. Treatment decision making in elderly patients in routine clinical practice is a challenge, particularly as not all patients fall into two distinct groups as described above. There is evidence from this series that some patients living beyond three years can maintain disease control longer-term, and as such adds to the difficulty in accurately advising patients as to the most appropriate treatment. Surgery has been shown to be safe with regional anaesthesia[42], allowing increasingly frail patients greater access to surgery, and as such should be the standard of care for operable breast cancer. PET with AIs in post-menopausal women may be a viable long-term alternative in the right circumstance and in the absence of failure risk factors. A specific prognostic index to identify the likelihood of treatment failure would give more objectivity in treatment planning, allowing the clinician to counsel the patient appropriately. However, no such model is yet widely available.
Generalisability	21	Discuss the generalisability (external validity) of the study results	21	
Other information				

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.