Patients electing to have PET rather than surgery for operable breast cancer are a high risk of treatment failure

1. First and corresponding author:

Robert Thomas

Specialist Trainee General and Breast Surgery

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

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

Consultant Oncoplastic Breast Surgeon

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

4LP

Email: henry.cain@nuth.nhs.uk

ABSTRACT

Background

Primary endocrine therapy (PET) is a treatment option for elderly patients with ER positive breast cancer enabling frail patients to avoid surgery. As a long-term treatment option it has been shown to be inferior to surgery in controlling local disease. Decision making in these patients is crucial in avoiding treatment failure. We examined the influence of decision-making on outcomes of PET failure as a secondary analysis as part of a large observational study.

Methods

Consecutive patients treated with PET between 2005 and 2015 for operable breast cancers were included in a retrospective observational study in 3 breast centres in the North-East. Treatment decision processes were examined by case note review and outcomes of treatment success or failure recorded.

Results

488 patients were included with mean follow up 31 months. Overall 63 (12%) experienced treatment failure. 227 (46.6%) were given a choice between surgery and PET at diagnosis. Logistic regression identified older age [OR 0.94 (0.91 to 0.96) p <0.001] and reduced mobility [OR 0.6 (0.37 to 0.97) p 0.036] to be less likely offered surgery. Those offered surgery were more likely to experience treatment failure with PET [SHR 1.78 (1.05 to 3.02) p 0.033].

Conclusions

Despite a low failure rate in our series (literature failure rates vary between 12 and 85%), these results suggest that those actively offered a choice between surgery and PET are at greater risk of failure when choosing PET.

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Keywords

Primary endocrine therapy; breast cancer; elderly

BACKGROUND

Primary endocrine therapy (PET) is an effective method of treating oestrogen receptor [ER] positive breast cancer in older patients, enabling some to avoid surgery. [1,2] No difference in overall survival has been shown in comparison to surgery, but longer-term local disease control is inferior with PET [3]. PET use in the UK is common [4], with evidence that increasing age is strongly associated with non-surgical treatment [5].

Advances in the medical care of geriatric patients has resulted in patients with ever increasing co-morbidities living longer, making decisions in this cohort with operable breast cancer increasingly challenging [6]. Current guidance suggests early involvement of Care of the Elderly (COTE) Physicians in managing these patients [7], however utilisation in the UK is low or access limited [8].

Our own observational study investigating failure of PET reflected current UK practice with only 9.4% and 1% of patients receiving an anaesthetic opinion or geriatric assessment respectively. Decision-making was therefore largely lead by the surgeon. [9] It is unknown what direct effect decision-making has on the outcome of PET. The aim of this study was to assess how decision-making processes in older patients with breast cancer treated with PET may impact on the risk of treatment failure. In particular, we wanted to determine whether patients who were offered a choice between surgery or PET but who elected for PET were at a disadvantage in comparison to those who were advised PET by their clinician.

METHODS

This study is a secondary analysis from a previously published observational study investigating treatment failure on PET. This was performed on patients with ER positive early breast cancer treated with PET between January 2005 and December 2015. Patients were identified from the local Multi-disciplinary team (MDT) databases of three North-east of England breast cancer-screening units. Exclusion criteria were: patients with inoperable or metastatic disease at presentation, or if endocrine therapy was given as neo-adjuvant treatment prior to surgery; ; and patients whose follow up was performed at a different unit, having been diagnosed initially in one of the three major units. Data collection was retrospective.

Decision-making

Healthcare records were studied, in particular outpatient clinic notes, to find evidence of whether patients were given a choice between surgery and PET or not. All decisions were ratified in the local multidisciplinary team meeting (MDTM).

Patient and disease characteristics

Co-morbid disease and evidence of disabilities were recorded from the healthcare records. Tumour information that included tumour sub-type, grade, receptor status, lymph node involvement and size was documented from the case-notes or the respective hospital-based computer reporting systems.

Follow-up

Patients were followed up until death, or were still under follow up at the censor point (December 2015). Whilst under follow up, patients were reviewed periodically in the outpatients department.

Outcome measures

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.

Statistical analysis

Characteristics between those who were offered a choice of treatment to those who were not were compared with the Chi-squared test or fisher's exact test where appropriate. Logistic regression was also used to identify factors that were independently associated with being offered surgery. Backwards selection was used with variables with $p<0.1$ removed from the model. Lastly, the association between being offered surgery and risk of death without failure and of treatment failure were explored using competing risks analysis. Results are presented as sub-hazard ratios (SHR) with 95% confidence intervals (CI). Analysis was carried out using STATA 14IC.

RESULTS

As detailed previously, 488 patients that were treated with PET were followed for a total of 1271 person years. Among all patients the median follow up was 28 (5 to 41) months. Among 232 patients who died median follow up was 21 (10 to 36) months. The remaining 255 patients were alive at the end of December 2015 by which time they had provided a median follow up of 32 (21 to 45) months. Treatment adherence data was excellent amongst almost all the cohort, with 480 fully compliant with treatment. No patients switched to surgery on the basis of poor drug compliance. Only 8 patients (1.6%) were lost to follow up prior to their death and so data on their adherence is missing.

Treatment decisions

227 (46.6%) of patients were offered a choice between surgery and PET. The majority (53.4%) were not offered surgery and advised PET by the clinical team. Characteristics of patients who were and were not offered surgery are summarised in table 1. Those offered a choice between surgery and PET were significantly younger and had smaller tumours. A past history of stroke, impaired mobility, cognitive dysfunction and nursing home residency were all associated with allocation of PET without choice.

Logistic regression was also used to identify factors which were independently associated with being offered surgery. Backwards selection was used with variables with $p<0.1$ removed from the model. The final model is summarised in

table 2. Older age and reduced mobility were the only variables independently associated with reduced odds of being offered surgery.

Impact of treatment choice on outcome

Lastly, the association between being offered surgery and risk of death without failure and of treatment failure were explored using competing risks analysis with the results summarised in table 3. Those offered surgery were significantly less likely to die without failure SHR 0.35 (0.26-0.46) $p<0.001$. The relationship between being offered surgery and dying without failure was significant SHR 1.78 (1.05-3.02) $p=0.033$ after adjusting for all factors previously found to be associated with death without failure, treatment failure or likelihood of being offered surgery.

DISCUSSION

A majority of patients in our cohort were advised against surgery and were allocated PET by their clinician. These were more likely to be older and frailer patients. Younger patients with smaller cancers had a greater chance of being offered surgery. Those patients who were given the option of surgery but chose to have PET were less likely to die with controlled local disease.

These results are important as this is the first study to examine how initial treatment recommendations and decisions for PET in older patients with breast cancer may impact on the outcome. It suggests that those patients who are offered a choice of treatment but elect to have PET may be at greater risk of

failure. These tended to be younger patients with probably a longer life expectancy, and therefore more likely to live beyond the time-dependent window of local control that PET provides.

Rates of non-surgical treatment of breast cancer in older patients in the literature are variable [10]. Increasing age, tumour size, disability and co-morbidity have been associated with greater PET use. [5] Our results support this finding in that increasing age and poor mobility were independently associated with PET treatment without the offer of surgery. Interestingly, in our original analysis, large tumour size was an independent risk factor for treatment failure, yet these patients were less likely to have been given a treatment choice. One explanation for this is that larger tumours are more likely to require mastectomy [11] and there may be an aversion from surgeons to submit patients to a more morbid procedure. Additionally, surgeons are less likely to adopt oncoplastic techniques to facilitate breast conservation in large tumours in these patients for potential fear of increased post-operative complications. [12] Unsurprisingly, the recent National audit of breast cancer in older patients has shown declining rates of surgery with increasing age, frailty and co-morbidity. [8]

Despite the lack of treatment choice in the majority of our cohort, the original analysis revealed a low overall failure rate of PET in comparison to that in the literature. This may suggest that the clinicians allocating treatment were generally successful in identifying patients who should be treated without surgery. In patients who had a choice of treatment, there is evidence that in the

absence of certain risk factors for failure (such as large tumour size, lymph node metastases and high histological grade), local disease control with PET can be maintained long term.[9] Whilst it is beyond the scope of this study to explore the reasoning behind patient's decisions, the younger fitter patients who were offered surgery may choose non-operative management for fear of loosing independence as a result of surgery. It is clear from the first analysis however, that patients had limited input from geriatrics or anaesthetics with respect to help with decision-making.

The results from this study have relevance to clinical practice as they suggest that if surgery is an option for a patient but they choose PET, they are at potential risk of treatment failure. This implies that if a patient is deemed fit enough for surgery, PET may not be the most effective long-term option for them. This is not to suggest a patient should not be given a choice, but advised appropriately. Decision-making processes are complex, but many are made in a time-pressured outpatient clinic. UK cancer waiting time targets allow little room for movement, particularly if additional clinical opinions are needed. The International Society of Geriatric Oncology (SIOG) advises geriatric involvement in the management of older patients with cancer [7], yet the recent national UK audit in older patients with breast cancer (NABCOP) revealed teams caring for older patients (TCOP) rarely attended breast cancer MDTM's. 47% of UK units have no formal service for this, with few providing a formal assessment of frailty, co-morbidity and cognition beyond classical 'history and examination'. Nationally there is much variation in the management of older patients with cancer and seemingly no standard approach.

Recruiting elderly patients into experimental studies has proven difficult in the past [13], and so observational studies such as the bridging the age gap trial [14] , NABCOP and this will and do provide useful clinically relevant evidence. This study does have its limitations however, with the main one being retrospective data collection and reliance on medical records. Outpatient letters tended to be variable in their detail, and data was dependent on the accuracy of the clinician's account as a true reflection of events. Where detail was lacking, nursing notes including those from specialist nurses, were studied for information to offset this. There is also a degree of selection bias in this cohort with respect to HER 2 positive disease, with few numbers in either group and so few conclusions can be drawn with regards to these patients. This is likely due to evidence that HER2 positivity is a risk factor for early failure on PET [15] and so most of these patients would have had surgery in the first instance. The excellent treatment compliance doesn't necessarily reflect that of endocrine therapy in the adjuvant setting. [16] This may because it was the only breast cancer treatment these patients were receiving and so patients persisted with treatment despite any poor drug tolerance. In addition, this study does not provide a direct comparison with surgery in outcomes, as it only concerns patients receiving primary endocrine therapy from the outset. No data is therefore available for patients who elected to have surgery initially as that was not the purpose of the original observational study. Previous RCTs [17] and a subsequent Cochrane review [3] have addressed that question. What this study addresses is the potential problems faced by elderly breast cancer patients if they opt for PET over surgery, which would arguably be the better long-term option.

This study has shown the first evidence on how outcomes of PET may be influenced by pre-treatment decision-making. It suggests that ER positive patients who are offered surgery but choose PET may be at risk of losing local control of their disease. The ongoing large national cohort studies and audits should provide tools in the future to assist in the management of this often-difficult patient group. They should also help highlight the need to healthcare providers and regulatory bodies for universal access to TCOP's in breast cancer care.

Tables and figures

Table 1. Comparison of characteristics in the two groups: patients not offered surgery and those offered surgery.

	Not offered surgery	Offered surgery	p-value
Total	260	228	
Age at diagnosis, median (IQR)	85(81 to 90)	82(76 to 86)	<0.001
Tumour size, median (IQR),	27(20 to 35)	25(18 to 34)	0.006
Bilateral disease, n (%)	9(3.5)	13(5.7)	0.230
HER2 Pos, n (%)	19(9.3)	13(6.5)	0.309
TPM grade, n(%)			
1	26(10.5)	23(10.5)	0.575
2	187(75.4)	173(78.6)	
3	35(14.1)	24(10.9)	
Strength ER positivity, n(%)			
3-4	3(1.1)	2(0.9)	0.684
5-6	5(1.9)	7(3.0)	
7-8	252(96.9)	218(96.0)	
Avilla involvement, n(%)	60(23.4)	54(23.8)	0.909
Vascular invasion, n(%)	16(6.4)	16(7.2)	0.737
Associated micro-calcification, n(%)	35(13.8)	30(13.5)	0.904
Histological subtype			0.519
IDC	195 (77.1)	179 (80.3)	
ILC	38 (15.0)	32 (14.4)	
Other	20 (7.9)	12 (5.4)	
Prev unrelated Breast cancer, n (%)	17(6.6)	14(6.3)	0.899
IHD, n (%)	131(50.8)	115(51.6)	0.862
Cardiac failure, n (%)	63(24.3)	56(24.7)	0.841
Stroke, n (%)	72(27.8)	42(18.8)	0.021
Sig pulmonary disease, n (%)	72(27.8)	67(30.0)	0.587
Diabetes, n (%)	42(16.2)	31(13.9)	0.480
Long term steroids, n (%)	4(1.5)	6(2.7)	0.525
Co-morbidities*, median (IQR)	1(1 to 2)	1 (1 to 2)	0.482
0	62 (23.9)	58(25.6)	0.818
1 to 2	147(56.5)	129(56.8)	
3 or more	51(19.6)	40(17.6)	
Impaired mobility, n (%)	202(77.7)	147(64.8)	0.002
Cognitive impairment, n (%)	105(40.5)	29(12.9)	<0.001
Carers at home, n (%)	76(29.3)	52(23.1)	0.121
Nursing home resident, n (%)	111(42.9)	25(11.1)	<0.001

Table 2: Independent predictors of being offered surgery

	Odds ratio	95% CI	p-value
Age at diagnosis	0.94	0.91 to 0.96	<0.001
Reduced mobility	0.60	0.37 to 0.97	0.036

Table 3: Hazard of dying without failure and of treatment failure in patients offered surgery

	Event = Death with disease controlled			Event =Treatment failure		
	SHR	95% CI	p-value	SHR	95% CI	p-value
Unadjusted	0.35	0.26 to 0.46	<0.001	1.52	0.93 to 2,49	0.094
Adjusted*	0.35	0.26 to 0.47	<0.001	1.78	1.05 to 3.02	0.033

*Adjusted for age, tumour size, number of comorbidities, TPM grade, axilla involvement and reduced mobility

Declaration of Interests statement

HC receives honorariums and travel expenses from Roche Products Limited, Pfizer Inc. and Baxter Healthcare; 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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