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Introduction

Breast cancer is a common condition; the incidence of which increases with age. In the United Kingdom over 40,000 women are diagnosed with breast cancer annually and 30% of these are aged 70 or older. A number of studies have clearly demonstrated that older patients do not receive standard approaches to either local or adjuvant treatment¹⁻⁶. More recent studies demonstrate that it is the group of women over the age of 75 or 80 at diagnosis who are failing to receive standard therapy.⁷ There are very few research trials to inform the surgical management of such patients. There is evidence that this under treatment results in a significantly worse prognosis (Fig 1).⁸ There is an emerging consensus that older women should be managed in a similar fashion to younger patients with regards to surgical treatment,⁹ but special consideration should be given to those patients who, (through reasons of co-morbidity or extreme age), have a very limited life expectancy. In such cases consideration may be given, after appropriate multi-disciplinary assessment, to alternative approaches. The factors influencing these decisions are reviewed herein.

Tumour biology and stage at presentation.

As reviewed elsewhere in this special edition of Clinical Oncology there is evidence that the biological behaviour of breast cancer may be more favourable in older patients with an increased proportion of tumours demonstrating oestrogen receptor positivity and a reduction in the incidence of HER2 expression.¹⁰ However, these favourable characteristics may be offset by a later stage at presentation: Older patients present with larger

primary tumours and an increased incidence of locally advanced and metastatic disease. Some studies demonstrate an increased incidence of axillary node positivity whilst others report a reduced incidence of axillary node involvement.^{11,12} The reasons for later stage at presentation may relate to reduced screening uptake,^{13,14} and patient related delays in diagnosis, possibly partly due to reduced breast awareness.¹⁵

Impact of breast cancer on survival in older women

Until the late 70's standard management of elderly breast cancer patients relied on surgical excision of the primary¹⁶ until a publication by a Scottish research group proved the efficacy of Tamoxifen in this age group.¹⁷ This approach rapidly gained acceptance and in the 1980's the prevailing view in the United Kingdom and some other countries was that a diagnosis of breast cancer in patients over the age of 70 had little or no impact on survival. This view, combined with the concept that breast cancer was a systemic disease at diagnosis, resulted in a significant reduction in the rates of surgical treatment of primary breast cancer in women over the age of 70.

There is evidence that survival in older women with breast cancer is substantially worse than in younger women.⁵ Whilst a significant proportion of this mortality may be due to deaths from competing causes breast cancer will be the most likely cause of death in the majority of patients with this diagnosis. The exceptions are women with significant co-morbidity or at the extremes of older age who have a reduced life expectancy of less than 5 years.^{6,18}

There is little known about survival outcomes in older breast cancer patients, other than that overall survival is substantially worse due to the increased incidence of non-breast cancer deaths. Breast cancer specific mortality in this age group is much more difficult to determine from the literature. This is due to the fact that outcomes are rarely adjusted to reflect patient co-morbidity, there is widespread disease under-staging in older women as many either have no surgery or limited surgery, (often excluding axillary staging) and lastly, treatment is often non-standard compared with younger patients. All of these factors result in inaccurate or misleading comparisons with younger women's' outcomes. Further research is therefore required to define the precise relationship between age of diagnosis and survival in breast cancer.

Impact of age on suitability for surgical treatment

Ageing has significant effects on normal physiological processes independent of any associated disease processes, (senescence). These include reductions in cardiac, respiratory and renal reserve in addition to an increased incidence of cognitive impairment. These factors alone may serve to limit quality of life and suitability for certain adjuvant treatments such as cytotoxic chemotherapy. However, the morbidity associated with surgery for breast cancer is minimal and these physiological considerations are rarely a significant factor in determining whether a patient should be considered eligible for surgical treatment.¹⁹

In addition to the above mentioned senescent organ impairment, co morbid diseases are increasingly common with age and may significantly impact on

life expectancy and treatment tolerance.^{6,18} A number of scoring systems have been developed to predict life expectancy and guide treatment decision-making in the elderly. These include the Charlson Index which combines the number and severity of a defined selection of co-morbid diseases and can predict mortality with modest accuracy.²⁰ More recently tools such as the Comprehensive Geriatric Assessment and the Multidimensional Assessment for Cancer in the Elderly (MACE) have been developed. These include a detailed assessment of co-morbidity, functional status, cognitive function and depression scores.^{21,22} Measures of global functional ability have also been shown to be independently useful in predicting life expectancy. For example, the Activities of Daily Living (ADL), the Instrumental Activities of Daily Living (IADL) and the Mini Mental State Examination (MMSE) scores have all been shown to have prognostic value.²³⁻²⁵ These tools are relatively time consuming to administer and require specialist interpretation and may be outside the experience of most surgeons treating breast cancer. They are best utilised in the assessment of frail elderly patients where initial screening in a standard breast clinic indicates that life expectancy may be limited raising questions about the choices and efficacy of treatment.

Does surgical treatment improve survival and local control in older women with breast cancer?

Until the 1980's the standard treatment for breast cancer included surgery in almost all patients. The concept that endocrine therapy with tamoxifen could be an alternative to surgery for older women with breast cancer was proposed in the UK in 1982.¹⁷ This was based on the fact that 80% of older patients had

oestrogen receptor positive tumours and would be therefore respond to treatment with tamoxifen. This, combined with the high incidence of life limiting co-morbidity, formed the rationale for this approach. A number of randomised trials comparing endocrine therapy with tamoxifen versus surgery (either with or without adjuvant tamoxifen) were subsequently performed. These studies have recently been systematically reviewed and some subjected to meta-analysis.²⁶ Seven randomised trials were included in the analysis. All these studies recruited women over the age of 70 with operable breast cancer who were fit for surgery under general anaesthesia. Endocrine treatment was with tamoxifen and most of the studies failed to assess oestrogen receptor status of the tumours. Three studies^{27 28,29} compared surgery without adjuvant tamoxifen to tamoxifen alone. Four studies^{30 4,31,32} compared surgery with adjuvant tamoxifen to tamoxifen alone. Surgery included mastectomy or wide local excision with or without radiotherapy combined with axillary clearance or staging in most of the trials. Overall the studies demonstrated that endocrine therapy alone is inferior to surgery with adjuvant endocrine therapy for the local control of breast cancer in this group of patients. However, the meta-analysis demonstrated no significant difference in overall survival between the two treatments. One of the trials showed a small but significant survival advantage for surgery at 13 years follow-up.³⁰ Despite the lack of clear evidence of survival benefit for surgery, the clear advantage in local disease control has resulted in a reduction in the use of primary endocrine therapy in this population of women. However recent audits demonstrate the continued use of primary endocrine therapy in a substantial proportion of older (over 80 years), less fit patients

with breast cancer in the United Kingdom.^{2 3,7} These studies demonstrating the continued use of primary endocrine therapy in a substantial proportion of older women are at variance with the results of a survey of UK breast surgeons 98% of whom state that age alone is not relevant in offering surgery for the treatment of breast cancer. However 34% of respondents acknowledged that the patient's biological age is a significant factor although less than half utilise any form of assessment of fitness with only a very small minority using tools such as comprehensive geriatric assessment.³³ These findings demonstrate that while surgeons in the UK are open to treating older patients with standard approaches including surgery they frequently fail to do so predominantly due to concerns about the patient's fitness and overall life expectancy.

Less information is available on the rates of omission of surgery in other countries but recent publications indicate similar trends in other European countries.^{5,6} Despite the publication of a number of studies randomising patients to surgery or endocrine therapy and the continued widespread use of primary endocrine therapy, little is known about patient attitudes and choices in relation to these different options. Recent small qualitative studies in the UK demonstrate that this group of patients generally do not demonstrate strong preferences and tend to defer decisions about treatments to their physicians with overall high levels of satisfaction with either surgery or primary endocrine therapy.³⁴ Clearly there is a need for reliable evidence in this area and the ESTEEM trial is a large UK randomised controlled trial addressing these issues. In this study, patients aged 75 and over with primary, operable, oestrogen receptor positive breast cancer will be invited to join and are

randomised to receive primary endocrine therapy with an aromatase inhibitor (Anastrozole) or surgery and adjuvant Anastrozole. Importantly this study includes assessment of quality of life, patient preferences and cost effectiveness in addition to overall survival and control of local disease.

Until evidence from trials such as ESTEEM is available the appropriate management of older patients with breast cancer should include adequate surgery and appropriate adjuvant therapies in all patients. In the sub-set of patients with a predicted limited life expectancy, due to extreme age or co-morbidity, the surgical and adjuvant treatments may be modified or in some cases omitted. These approaches are discussed below.

Surgical approaches to the treatment of older patients with breast cancer: surgery to the breast

Primary breast cancer can be managed in the majority of cases by either mastectomy or wide local excision. Numerous studies demonstrate that the overall survival of these two approaches is equivalent. However the most recent overview analysis of the Early Breast Cancer Trialists' Collaborative Group demonstrates the importance of adequate local treatment in the management of primary operable breast cancer.³⁵ The overview evaluated the impact of radiotherapy in patients treated by either breast conserving surgery or mastectomy in terms of local control and long-term survival. There was a significant improvement in local control by the addition of radiotherapy to wide local excision in patients with lymph node negative and lymph node positive disease. Furthermore there was a significant benefit in local control by the

addition of radiotherapy to the chest wall in patients treated by mastectomy where there was axillary node involvement. The surprising finding of the overview was that there was a significant survival advantage at 15 years for patients treated with radiotherapy in addition to breast conserving surgery or mastectomy. The benefit in the mastectomy group was predominantly seen in patients with axillary node involvement whereas the survival benefit for patients treated by breast conservation was independent of nodal status. What is the significance of these findings for the management of older patients with breast cancer? The EBCTCG concluded that “in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided”. The implication of this for older women with breast cancer is that adequate local control of disease is important and may have a significant impact on survival in women with a life expectancy of between 10 to 15 years. Therefore for a healthy woman of 70 years of age with a predicted life expectancy of 15 years, treatment should follow standard guidelines based on evidence from trials recruiting younger women. However, in women of more advanced age or with associated co-morbidity where life expectancy may be restricted to less than 5 years it is reasonable to consider alternative approaches.

This question of adjuvant radiotherapy after breast conserving surgery in older women is addressed in the PRIME trial which aims to establish whether there is a cohort of older patients with low risk disease where radiotherapy can be omitted.

The current 'absolute' indications for mastectomy include primary tumours of 5cm or more in diameter and multi focal disease within more than one quadrant of the breast. Relative indications for mastectomy include smaller primary tumour size in patients with small overall breast size, patients with central tumours, multi-centric tumours in a single quadrant and patients with an extensive in situ component to their invasive cancer. A further important indication for mastectomy is patient choice. Large audits in the UK continue to demonstrate that a significant proportion of patients with small tumours who would be eligible for breast conservation surgery will choose mastectomy if given a choice.⁷

For patients with uni-focal ER positive primary cancers too large to consider breast conservation, neoadjuvant treatment with endocrine therapy can be utilised to reduce tumour size to permit breast conservation. In this neoadjuvant setting, Letrozole has increased efficacy compared to Tamoxifen, (55 versus 36% response rate.³⁶ Although there are no data to support the use of neo adjuvant chemotherapy in this patient group there are no theoretical reasons why this approach should not be considered in patients with larger, ER negative tumours. The role of oncoplastic approaches to permit breast conservation are discussed below.

Surgery to the axilla

The accurate assessment and treatment of axillary metastases from primary breast cancer is important for two reasons. Firstly, where there is clear clinical or biopsy proven nodal disease axillary clearance (or adequate

radiotherapy) following a sampling procedure is indicated to prevent local progression with the associated potentially distressing symptoms this can cause. The use of preoperative axillary ultrasound and biopsy of suspicious nodes is gaining acceptance. Routine axillary clearance has been superseded by less invasive approaches such as sentinel node biopsy or non-targeted 4 node sampling. Sentinel lymph node biopsy (SNB) comprises the injection of a radio-labelled colloid and/or blue dye into the breast prior to surgery. At surgery the radioactive and/or blue coloured sentinel nodes are identified and removed. Typically there are one or two such nodes and the use of a hand held gamma-probe (with or without pre-operative lymphoscintigram) reduces the extent of dissection substantially. The presence of metastases in these nodes is usually confirmed by post-operative standard histological assessment but per-operative frozen section, imprint cytology or molecular biology approaches can be undertaken with immediate completion axillary dissection where axillary nodal metastases are identified. A number of studies have demonstrated the accuracy of SNB and the improved quality of life associated with this approach when compared to axillary node dissection³⁷⁻³⁹ SNB is associated with a significant reduction in arm related morbidity (lymphoedema) and numbness without any associated increase in anxiety in comparison to the axillary node clearance group. In many ways the SNB approach is ideally suited to older patients where the potential morbidity associated with more radical axillary surgery may have a greater impact on arm function.

The second reason for assessing and treating axillary nodal disease is in the selection of adjuvant therapies including chemotherapy and radiotherapy. At present the evidence base for the use of chemotherapy in older patients is lacking and therefore some authorities argue that staging of the clinically (and/or ultrasound) uninvolved axilla is unnecessary. However other therapies may also depend on the extent of axillary nodal disease, particularly chest wall radiotherapy following mastectomy. Therefore in general older patients should undergo the same axillary staging and treatment approaches as employed in younger women. At present the utilisation of a completion clearance or axillary radiotherapy following a node positive SNB is a matter of local treatment preferences but are the subject of randomised clinical trials eg the AMAROS study.

Alternative approaches in patients with restricted life expectancy

There is a small sub-set of patients with a significantly reduced life expectancy of 2 to 5 years due to either extreme age or associated co-morbidity. As described above the increased use of tools such as Comprehensive Geriatric Assessment (CGA) allows these patients to be identified and clinicians who routinely treat breast cancer will be immediately familiar with such patients who may have extremely limited mobility, impaired cognitive function and significant cardiovascular, respiratory and/or renal impairment. Clearly in such patients the surgical treatment of breast cancer is unlikely to have any significant impact on life expectancy as these patients are more likely to die of causes other than breast cancer. However, surgical treatment may still be appropriate in such patients to avoid the development

of distressing symptoms, such as pain, ulceration and bleeding due to local disease progression. These approaches may include surgery under local or regional anaesthesia and the omission or modification of axillary surgery in patients where there is no evidence of axillary nodal disease. For instance a lower (level 1) axillary clearance may be preferable to SNB with subsequent clearance for node positive patients, where radiotherapy is not an option. In general terms, even in frail elderly patients, general anaesthesia is a safe option with a mortality of less than 1%.²⁵ Should a full anaesthetic assessment indicate that general anaesthesia may be associated with a significant risk wide local excision and even mastectomy can be performed under local or regional anaesthesia such as intercostal nerve block.^{40,41} The assessment of an anaesthetist experienced in the management of these frail patients is essential in the selection of the appropriate anaesthetic technique.

Axillary surgery may be omitted in patients with low life expectancy where surgery to the primary tumour may be performed under local anaesthetic. This has little impact on overall survival particularly in women aged 75 or over and studies indicate a local progression of less than 10%, which, in the majority of cases, can be controlled with either further surgery or radiotherapy.^{42,43}

As noted previously an alternative to surgery in patients with a reduced life expectancy and oestrogen receptor positive disease is primary endocrine therapy. This is particularly relevant in this subset of patients as the majority will experience a substantial reduction or complete disappearance of the

primary tumour and associated lymphadenopathy. The median duration of disease control with single agent hormonal therapy is 2-3 years, after which disease progression may occur in some patients. However further response to a change in endocrine therapy can be seen as the mechanism of drug resistance differs between tamoxifen and the aromatase inhibitors.

Complications of surgery

The mortality rate for breast cancer surgery is very low even in very old and frail women. Physical complications include scar formation, wound pain, seroma formation, haematoma, infection and skin necrosis following mastectomy. The complications of axillary surgery increase with the extent of node excision and includes seroma and haematoma, infection, paraesthesia and neuropathic pain, mammary oedema, shoulder stiffness and rarely damage to the long thoracic nerve resulting in 'winging' of scapula. The most significant complication of axillary node clearance is lymphoedema which may occur in up to 38% of patients.⁴⁴ Sentinel node biopsy and axillary sampling techniques are associated with a significant reduction in the risk of these complications although lymphoedema may occur even following sentinel node biopsy.³⁷ The incidence of these complications following surgery is not significantly increased by patient age or co-morbidity.⁴⁵

The psychological impact of the surgical treatment of breast cancer is well recognised and the evidence suggests that the psychological morbidity may be reduced in the long run by breast conserving techniques although the extent of this may be less substantial than initially anticipated.

The trials comparing primary endocrine therapy with surgery have afforded the opportunity to investigate the impact of surgery on psychological well being in women with breast cancer. This demonstrated a short-term negative impact of surgery on psychological well being at three months post operatively but by 2 years this difference had disappeared.⁴⁶

Breast reconstruction and onco-plastic surgical techniques

Over the last 10 years there has been a substantial increase in the rates of breast reconstruction following mastectomy. This has been associated with an increase in the range of approaches available for breast conservation such as therapeutic mammoplasty and breast re-shaping by volume displacement (known as oncoplastic surgical approaches). These new techniques have had a substantial impact in the management of women with breast cancer but to date the evidence indicates that older women, particularly those over the age of 70 years of age are not benefiting from breast reconstruction or oncoplastic approaches despite guidelines which indicate that these techniques should be widely available. There are a number of potential reasons for this, including patient and health care professional factors. Older patients may consider the physical impact of the surgical treatment of breast cancer less important than younger patients and have fewer concerns about body image.⁴⁷ However, body integrity is an important issue for some patients and some case series describe excellent results of breast reconstruction in older women. These report the results of techniques using autologous flaps (latissimus dorsi and Transverse Rectus Abdominus Myocutaneous, TRAM

flaps) although in general simple implant based approaches tend to be utilised more frequently in older women.^{48,49} In addition to patient factors the extremely low utilisation of breast reconstruction in women over the age of 75 may indicate that surgeons also have reservations despite the lack of an evidence base. There is no doubt that reconstructive techniques, particularly those utilising autologous myocutaneous flaps are more major surgical procedures which can be associated with an increased risk of side effects and complications such as flap necrosis. Studies in younger women indicate that these complications are more prevalent in patients with associated co-morbidity and it is this factor which is likely to be influencing surgeons and resulting in a failure to offer these options in the older population of women with breast cancer. Patients are also aware of these concerns and this may contribute to their decision not to seek breast reconstruction.⁵⁰ The national mastectomy and reconstruction audit being conducted in the United Kingdom will provide comprehensive data on this topic within the next few years.

A surgical management strategy for older patients with breast cancer

In general terms older patients should be considered for standard surgical approaches applicable to younger patients wherever possible. This should include the choice of breast conservation or mastectomy where appropriate and breast reconstruction or oncoplastic procedures should be included in the options available. The choice of surgical treatment should be decided in consultation with the patient after appropriate information has been made available. Following surgery adjuvant therapies including chemotherapy, endocrine therapy, radiotherapy and new agents such as Herceptin or

Lapatinib should be considered in accordance with standard protocols. The use of these adjuvant therapies is discussed elsewhere in this special edition. The axillary nodal status should be assessed in all suitable patients and nodal metastases should be confirmed by preoperative biopsy or sentinel lymph node biopsy techniques before proceeding to full axillary node clearance or radiotherapy for those patients with nodal disease.

In the subset of patients with impaired life expectancy due to extreme age or associated co-morbidity alternative approaches may be considered. These patients should be managed in consultation with specialist geriatricians and anaesthetists in addition to surgeons and oncologists. Appropriate assessment tools such as CGA should be utilised and patient preferences carefully sought. An algorithm for the management of these patients is outlined in figure 2.

Patients with ER positive tumours may opt for surgery or primary endocrine therapy. In this group of patients surgery may be performed under local or regional anaesthesia if patients are not fit for general anaesthesia.

The main aim of surgical treatment in these patients is to avoid the onset of distressing symptoms rather than to increase overall survival. It is therefore essential to include patient preferences in the decision making process and to undertake procedures which combine the minimum risk with the maximum achievable benefit in terms of avoiding morbidity either as a result of the surgical procedure or due to disease progression. In patients with proven

axillary node disease complete clearance should be considered but radiotherapy or primary endocrine therapy may be an alternative. In patients with a clinically node negative axilla a sentinel lymph node biopsy under local anaesthetic may be employed or axillary surgery omitted, particularly for patients on endocrine therapy with oestrogen receptor positive disease.

Summary of recommendations

This review of the surgical management of older women with breast cancer confirms the lack of adequate evidence base for the treatment of this group of patients. However, in the majority of patients with minimal co-morbidity and a life-expectancy of greater than 5 years standard surgical approaches can be recommended. For those patients with a reduced life expectancy rational modified approaches can be considered. In all patients careful consideration should be given to individual preferences. In patients with co-morbidity comprehensive assessment and the input of a specialist geriatrician and anaesthetist should be included in the decision making process. An individualised treatment plan should be developed in the context of an extended multi-disciplinary team. Ideally these patients will be managed in a specialist clinic setting with all the appropriate clinical specialists available to form an integrated assessment and treatment plan.²¹

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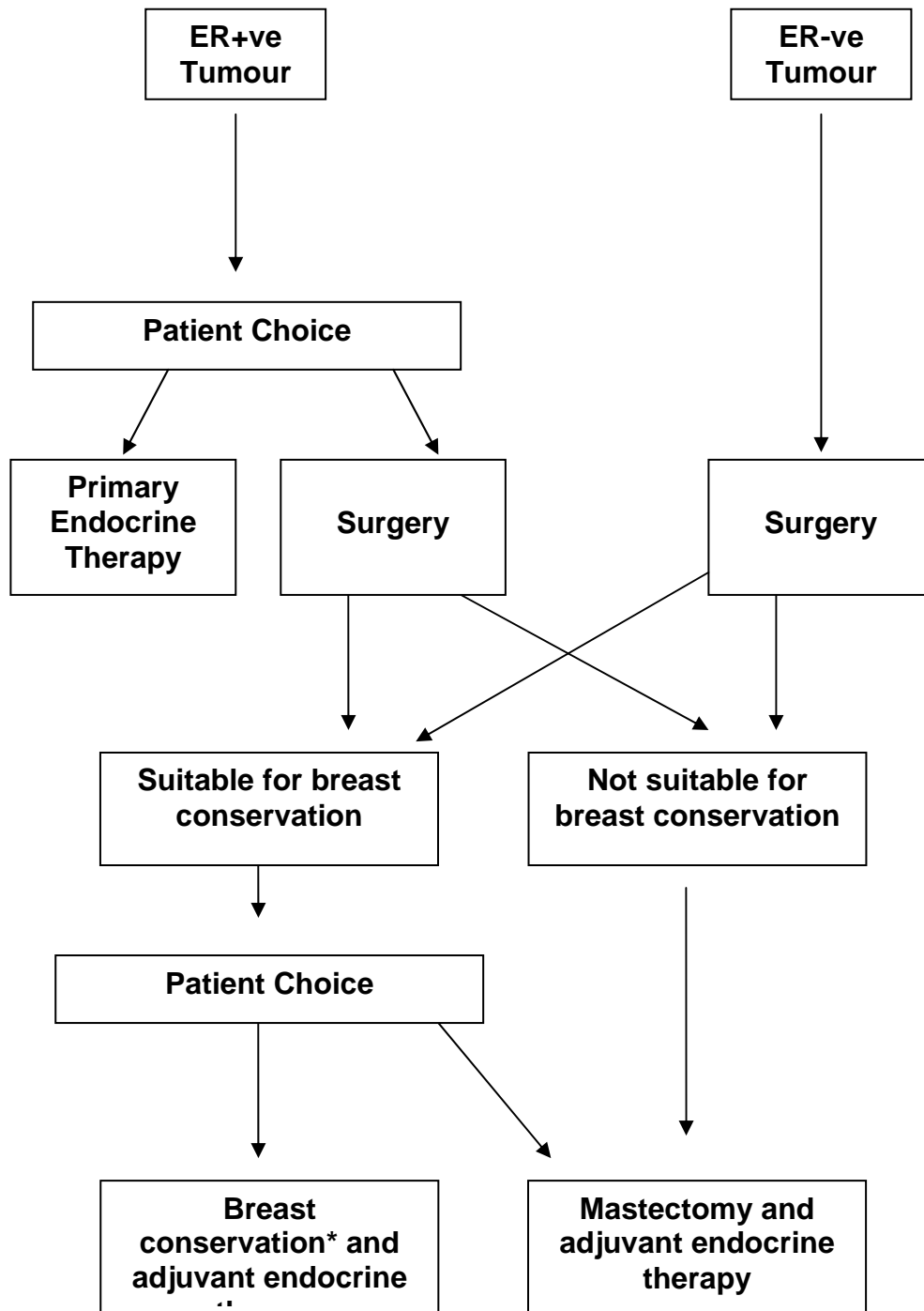
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Fig.2
Management of breast cancer in patients with limited life expectancy or not fit for surgery under general anaesthetic

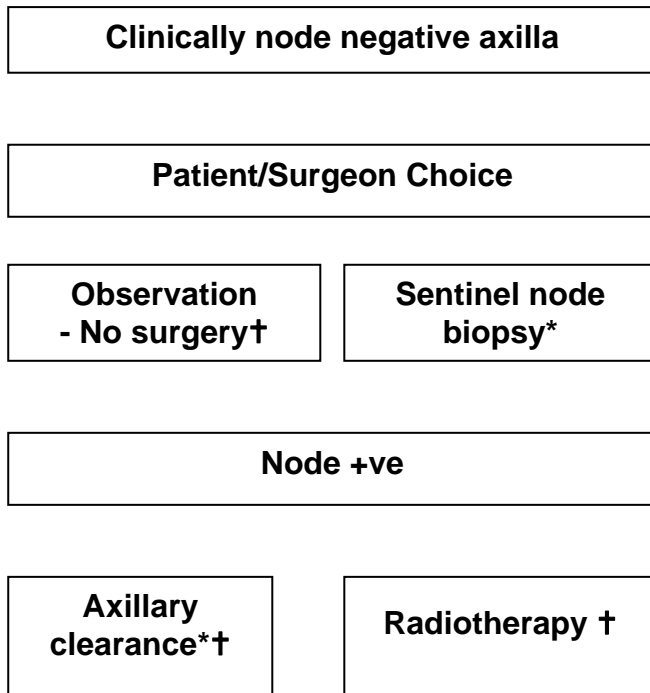
2a
Management of primary tumour



*surgery performed under local or general anaesthetic if appropriate

Fig 2b

Surgery to the axilla



***Under local or regional anaesthetic if appropriate
†With adjuvant endocrine therapy if ER+ve**

Fig. 1: Eurocare3/National Office of Statistics. Cases diagnosed from 1990-1994 followed up to 1999

