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Neoadjuvant endocrine therapy of breast cancer: a surgical perspective

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Abstract

Neoadjuvant treatment with chemotherapy or endocrine agents is being used increasingly to downstage locally advanced and large operable breast cancers. Following these treatments, inoperable breast cancer often becomes fully resectable, and initially operable tumours requiring mastectomy may be successfully removed by breast-conserving surgery. Patient selection is important to optimise neoadjuvant endocrine therapy: only patients with oestrogen receptor (ER)-rich breast cancer are candidates, and postmenopausal women are likely to benefit the most. Such patients can expect a high probability of responses over a 3-month treatment period. Response to therapy should be monitored by clinical examination as well as by ultrasound, mammography, or other imaging procedures. Third-generation aromatase inhibitors (letrozole, anastrozole and exemestane) are more effective than tamoxifen in this treatment setting. In a large randomised trial of neoadjuvant endocrine therapy in postmenopausal women, letrozole achieved significantly higher response rates than tamoxifen, and a correspondingly higher rate of breast-conserving surgery was possible in the letrozole-treated patients. There is some evidence to suggest that the nature of the tumour response is different for preoperative endocrine therapy compared with chemotherapy. This difference may result in a higher rate of complete tumour excisions following breast-conserving surgery after neoadjuvant endocrine treatment. There appears to be a low rate of subsequent local recurrence in patients having breast-conserving therapy after neoadjuvant endocrine therapy.

Keywords: Breast cancer; Neoadjuvant; Tamoxifen; Letrozole; Ultrasound; Mammography

1. Introduction

Despite improvements in early diagnosis of breast cancer, locally advanced disease (stage III) can account for up to 70% of breast cancer cases worldwide [1]. Early clinical experience indicated that neoadjuvant (preoperative, or primary) systemic chemotherapy often resulted in shrinkage of locally advanced and unresectable primary breast tumours, permitting their successful surgical removal [2,3]. Neoadjuvant therapy has been used more recently in patients with large operable breast cancers that would require mastectomy, but in whom tumour shrinkage can permit breast-conserving surgery [4,5]. In addition, when conservative surgery may initially be possible, but a significant volume of the breast would have to be removed, preoperative systemic therapy can permit less extensive resections to produce a better cosmetic result. Although neoadjuvant treatment successfully downstages breast tumours to render them operable, or to enable breast-conserving surgery, clinical outcome is not necessarily improved as a consequence. In a large randomised study comparing pre- and postoperative chemotherapy, no significant difference was found between those 2 groups of patients in either disease-free survival or overall survival [5,6].

Nevertheless, there are potential advantages to systemic neoadjuvant therapy of locally advanced breast cancer. The presence within the breast of a measurable mass allows a precise assessment of that patient's tumour responsiveness to a particular treatment. The early demonstration of tumour resistance can result in more efficient switching from an ineffective treatment to a potentially more effective therapy option. In addition, at least theoretically, treatment is initiated earlier, which should reduce the likelihood that resistant tumour cell variants will spontaneously emerge, or that occult micrometastases will grow.

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A major disadvantage of neoadjuvant therapy is the inability to evaluate the most important prognostic factor, axillary nodal status, which can only be determined at surgery. However, it is possible to preoperatively determine tumour grade and other vital tumour-related prognostic information, including hormone receptor status, from tumour core biopsies, and lymph node status determined after therapy retains its prognostic value.

There are some patients with locally advanced breast cancer for whom neoadjuvant therapy is contraindicated: those who have operable disease, but have multiple tumours, or those who have tumours which respond very slowly to treatment or in whom responses are difficult to discern. Patients with multiple operable tumours require mastectomy regardless of preoperative treatment success. Tumour types that should not generally be considered for neoadjuvant therapy because of difficulties in ascertaining the degree of response include many invasive lobular carcinomas or tumour types where a response defined as a reduction in tumour volume is not achievable within a reasonable time period such as invasive mucinous carcinomas.

Invasive lobular tumours have pathologically poorly-defined margins, which makes it difficult to judge tumour extent and accurate assessment of volume changes, either clinically or by ultrasound or mammography can be difficult. One such case is illustrated in Fig. 1: breast-conserving surgery was performed following 3 months of neoadjuvant tamoxifen, based on mammogram indications of tumour extent. Although a specimen X-ray indicated that the tumour had been completely removed, pathology revealed that cancer cells involved all surgical margins, and therefore this patient subsequently underwent a mastectomy.

The problem with invasive mucinous tumours is that they typically respond very slowly, perhaps because of large intratumoral mucin deposits. Fig. 2 shows such a tumour, which downstaged over 18 months and became operable by wide excision. The difficulty is that there was no apparent tumour response within the first 3–4 months, the standard length of neoadjuvant therapy.

2. Neoadjuvant endocrine therapy

Until recently, neoadjuvant therapy of breast cancer has mainly been limited to cytotoxic chemotherapy, but endocrine treatment is becoming an attractive alternative in hormone receptor-positive postmenopausal women, especially those who may not tolerate the toxicities of chemotherapy. To date, however, there have been few controlled studies of neoadjuvant endocrine therapy. In early studies with tamoxifen, patients were not selected for treatment on the basis of oestrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) status, which identifies those patients most likely to respond [7]. Nevertheless, one study concluded that tamoxifen provided an alternative preoperative treatment option for operable breast cancer in elderly patients [8]. Subsequent studies in postmenopausal ER+ patients demonstrated substantial tumour volume reductions over a 3–4-month treatment period using a variety of endocrine agents, including tamoxifen and the third-generation aromatase inhibitors, letrozole, anastrozole and exemestane [7,9–12].

A recent randomised trial (P024) compared 4 months of neoadjuvant treatment with either letrozole or tamoxifen in postmenopausal women with ER+ and/or PgR+ breast cancer. Evaluation of all patients indicated that letrozole achieved a significantly higher clinical response rate than tamoxifen (55% versus 36%; $P<0.001$), enabling significantly more letrozole-treated patients than tamoxifen-treated patients to undergo breast-conserving surgery (45 versus 35%; $P=0.022$) (Table 1) [12]. Median time to response was 66 days in the letrozole group and 70 days in the tamoxifen group. While fewer responses were demonstrated by ultrasound and by mammography, response rates were also significantly higher in the letrozole group than in the tamoxifen group. The only other factor, besides treatment, that significantly favoured breast-conserving surgery was smaller initial tumour size (T2 versus all other T stages; $P=0.0001$). In this study, letrozole was at least as well tolerated as tamoxifen [7,12].

In the P024 study, patient tumour responses to letrozole versus tamoxifen were also evaluated according to biopsy-confirmed assignment of ER and/or PgR status [7]. Both letrozole and tamoxifen achieved significantly more responses in patients with verified ER+ tumours than in patients with verified ER-negative tumours (Table 2). In both cases, response rates were higher for letrozole, reflecting the significantly better overall response rate for letrozole versus tamoxifen in biopsy-confirmed patients (60 versus 41%; $P=0.004$). Responses to letrozole were also significantly better for verified PgR+ tumours than for PgR-negative tumours, and there was a trend towards better responsiveness of PgR+ tumours to tamoxifen also. Differences in response rates between these 2 agents were most marked for tumours that were both ER+ and also positive for the markers ErbB-1 and/or ErbB-2 (letrozole 88% versus tamoxifen 21%; $P=0.0004$) [7].

An ongoing neoadjuvant study, designated IMPACT (IL34: IMmediate Preoperative Arimidex compared to Tamoxifen) is comparing anastrozole (1 mg daily) versus tamoxifen (20 mg daily) versus anastrozole plus tamoxifen. This is a multicentre, randomised, double-blind trial, with a target accrual of 330 patients that is being conducted in the United Kingdom and Germany. Patients are postmenopausal, with ER+ and/or PgR+ breast cancer that is large and operable (T2 or T3, N0–2, M0) or

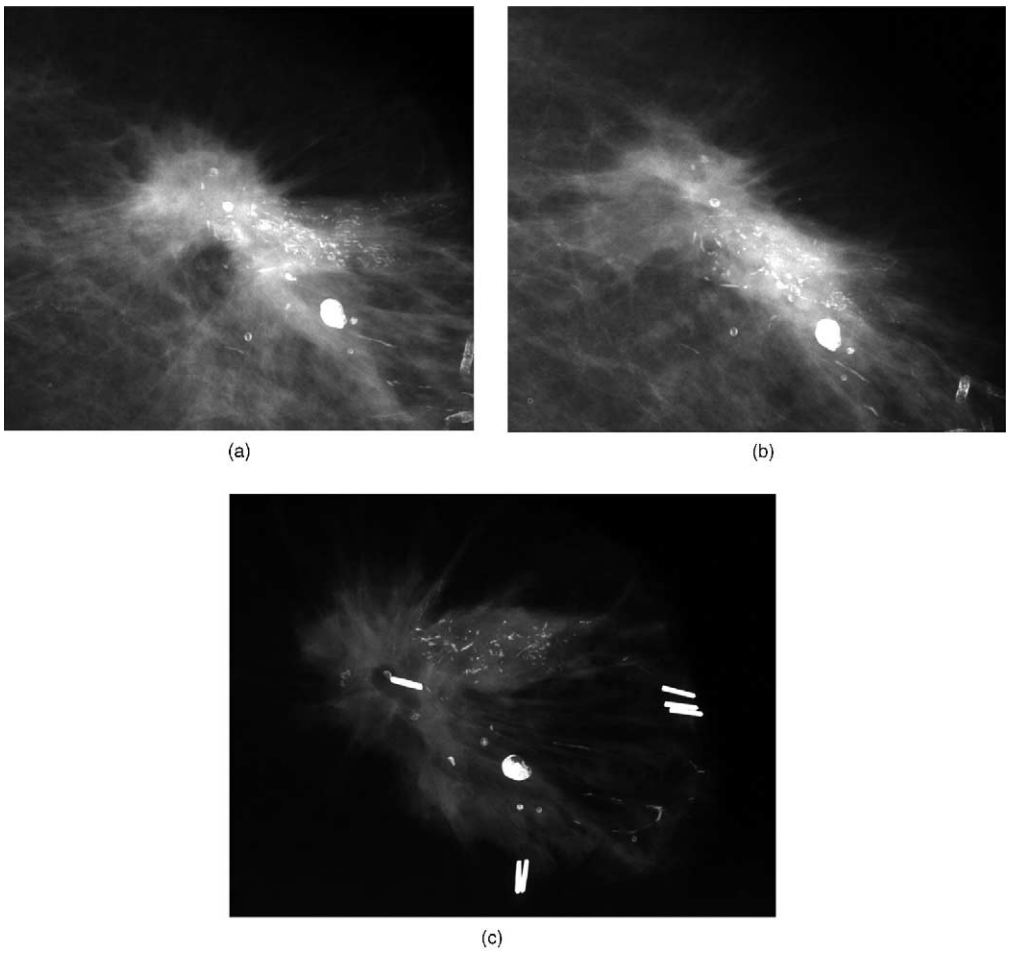

Fig. 1. A patient with invasive lobular carcinoma at diagnosis (a), after 3 months of neoadjuvant endocrine therapy with tamoxifen (b), and the specimen X-ray of the wide excision (c).

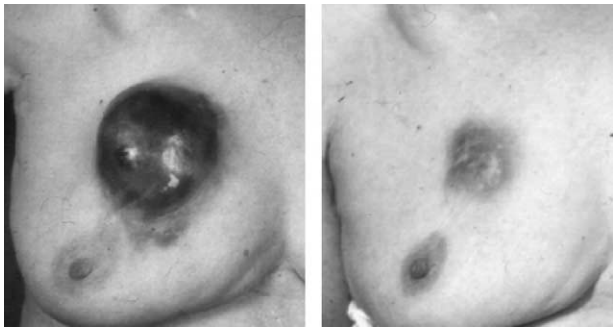

Fig. 2. A patient with a mucinous carcinoma before (a) and after (b) 18 months of endocrine therapy. The abnormality visible just under the clavicle is a lipoma.

potentially operable even if locally advanced (T4b, N0–2, M0). Treatment is for 3 months before surgery and then the same endocrine treatment is given in responders as adjuvant therapy for 5 years. Primary efficacy end points are objective tumour response at 3 months; secondary end points are breast conservation rate, assessment of several key biological markers (Ki-67, ER, PgR, and apoptotic indices), and safety. This study should complete accrual by the end of 2002.

3. Patient selection for neoadjuvant endocrine therapy

Although studies to date have failed to show any survival advantage in patients receiving neoadjuvant compared with adjuvant chemotherapy [5,6], there could nevertheless be benefits from neoadjuvant endocrine therapy provided there was more appropriate patient selection. When selecting patients for endocrine treatment, ER+ status, and, to a lesser extent, PgR+ status, are important determinants of response (incidence and extent of tumour shrinkage) [7]. There is some evidence of a direct correlation between the degree of ER expression and the incidence and extent of tumour response [13]. For that reason, the only patients selected for neoadjuvant therapy at the Edinburgh Breast Unit are those with ER-rich tumours [14]. This is true not only for postmenopausal patients, but also for premenopausal women treated by neoadjuvant endocrine therapy.

Table 1
Primary and secondary efficacy end point results of trial P024 comparing 4 months of neoadjuvant letrozole versus tamoxifen, in all study patients [12]

Efficacy end points	Letrozole ($n=154$) (%)	Tamoxifen ($n=170$) (%)	P value
Primary end point			
Clinical response (palpation)	55	36	<0.001
Complete	10	4	
Partial	45	32	
Secondary end points			
Ultrasound response	35	25	0.042
Complete	3	1	
Partial	32	24	
Mammographic response	34	16	<0.001
Complete	4	0	
Partial	30	16	
Breast-conserving surgery	45	35	0.022

ER-rich tumours can be characterised by several criteria. In the P024 randomised trial of preoperative letrozole versus tamoxifen, clinical responses were related to level of ER expression as determined by immunohistochemistry (IHC) using the semiquantitative Allred scoring system (0–8 on an ascending scale). There were no tamoxifen-induced responses at ER levels below a score of 6, in contrast to letrozole-induced responses of >30% at a score of 3 (Fig. 3). These results justify the cutoff guidelines for treating only patients with ER-rich breast cancers with neoadjuvant endocrine therapy in the Edinburgh Breast Unit: ⩾20 fmol/mg cytosolic protein, a histoscore of ⩾80, or an Allred score of ⩾6.

4. Assessment of response to neoadjuvant therapy

In evaluating patients for tumour downstaging by neoadjuvant therapy, there are a variety of procedures available for measuring tumour size or volume changes during treatment, including clinical examination (caliper measurement), mammography, ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography (PET). In practice, rather than relying on clinical assessment alone, patients receiving neoadjuvant therapy should be monitored by one or more imaging procedures. Comparative studies of clinical, mammography, and ultrasound measurements have found that tumour size and volume changes were most accurately measured by ultrasound, in that ultrasound results were the best predictor of response and correlated best with the final tumour size determined by pathology [10,15]. MRI and PET scanning are now often used, especially to monitor early reductions in tumour blood flow, which can signal the beginning of a significant tumour response.

Table 2
Responses in trial P024 comparing 4 months of neoadjuvant letrozole versus tamoxifen, relative to confirmed ER and/or PgR status [7]

Agent	Marker status	Response rate (%)	P value
Letrozole	ER+	60	0.005
	ER−	19	
	PgR+	63	0.018
	PgR−	41	
Tamoxifen	ER+	40	0.031
	ER−	11	
	PgR+	43	0.076
	PgR−	28	

ER, oestrogen receptor; PgR, progesterone receptor.

In neoadjuvant endocrine therapy of breast cancer, partial tumour responses are common, but complete responses confirmed pathologically occur infrequently [16]. Standard criteria for assessing response have been issued by the International Union Against Cancer (UICC), but these guidelines require a reduction in tumour volume to be maintained for 1 month. World Health Organization (WHO) response criteria are less stringent, specifying that a ⩾50% reduction in bidimensional measurements is required for a partial response, but without the 1-month maintenance period [17]. An alternative approach is to measure the reduction in tumour volume clinically or by mammography, with volume estimated from two 2-dimensional measurements taken at a 45° angle from each other, and applying the formula: $V=D^3\times\pi/6$ (D, mean diameter). Ultrasound volumes are calculated using two diameters as well as measured depth, using the formula: $V=D^2\times d\times\pi/6$ (d, mean thickness or depth).

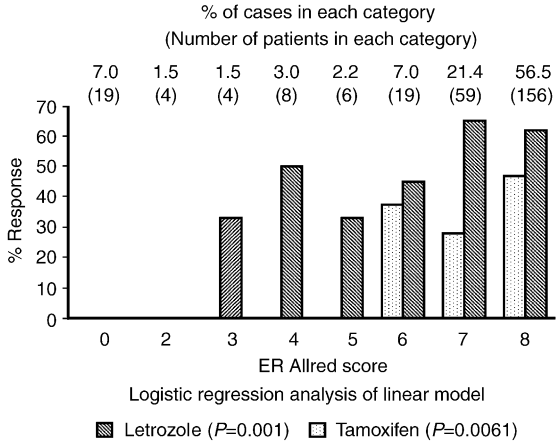

Fig. 3. Clinical response rate versus ER Allred score for letrozole and tamoxifen in the P024 randomized trial. Reprinted with permission from Lippincott, Williams and Wilkins [7].

5. Duration of neoadjuvant endocrine therapy

Standard practice has been to administer neoadjuvant chemotherapy for between 3 and 6 cycles (3–4 weeks per cycle) prior to surgery, a time period sufficient to distinguish responders from non-responders [1]. For those patients who do respond, treatment may permit either successful surgery for initially inoperable disease or more conservative surgery for tumours initially suitable only for mastectomy. The optimal duration of neoadjuvant endocrine therapy, however, has not been established. In early studies, patients usually remained on tamoxifen until their tumours became unresponsive and grew [8,18]. In unpublished studies that we have performed, 3 months was identified as the most appropriate length of preoperative treatment. This was determined in a consecutive series of 100 patients who were more than 70 years old and who had ER-rich breast cancers (>20 fmol/mg of cytosolic protein). After 3 months of tamoxifen, 73 patients had responded, based on a $>25\%$ ultrasound tumour volume reduction, and 1 patient had progressing disease. The remaining 27 patients were continued on tamoxifen for an additional 3 months, and during that period 18 remained static, 4 responded while 5 progressed. From these data, it is evident that if a patient has not responded within 3 months, then the subsequent poor response-to-progression ratio does not warrant more prolonged treatment. At this stage of treatment, resistance to tamoxifen seems to offset any further benefit. Therefore, in Edinburgh, 3 months of preoperative endocrine treatment has become the standard.

6. Response and downstaging of breast cancer

Response rates to preoperative chemotherapy are generally around 80% regardless of the regimen used [19]. In appropriately selected patients, neoadjuvant endocrine therapy also produces significant responses, especially using the third-generation aromatase inhibitors, as seen in a series of our patients (Table 3: incidences; Fig. 4: median tumour volume reductions). In these studies, response rates to letrozole, anastrozole, and exemestane were considerably greater than those previously recorded for tamoxifen. In the P024 randomised trial comparing letrozole and tamoxifen, letrozole was confirmed to be superior, with significantly higher response rates by clinical, ultrasound, and mammographic criteria (Table 1) [12].

In the Milan study, preoperative chemotherapy enabled breast-conserving surgery in 91% of patients, including 73% of those with tumours initially >5 cm in size [19]. A large trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP-B18) randomised patients to either neoadjuvant or adjuvant chemotherapy [5]. Of the 1523 neoadjuvant patients, 36% had a clinical complete response and 43% had a partial response, for an overall response rate of 79%; 25% of complete responders were free of tumour by pathological examination. Neoadjuvant patients in that study were significantly more likely than adjuvant patients to have a lumpectomy (68 versus 60%; $P<0.01$), although the difference was not as large as that seen in other studies [19–21].

An important consideration in neoadjuvant therapy is the relationship between tumour response and prognosis for long-term survival. We have shown that patients in whom tumour volume was reduced by at least 50% within 90 days of the beginning of neoadjuvant therapy survive significantly longer than patients experiencing less or no volume reduction within that period ($P<0.05$) [22].

There are few data on the success of preoperative endocrine therapy in converting patients from requiring mastectomy to successful use of breast-conserving surgery. Early results obtained at the Edinburgh Breast Unit did indicate that aromatase inhibitors were superior to tamoxifen in that regard (Table 4) and have been confirmed by the P024 trial; letrozole treatment enabled conservative surgery to be performed in significantly more patients than was possible in patients following tamoxifen treatment (45 versus 35%; $P=0.022$) (Table 1) [12].

7. Completeness of tumour excision and incidence of local recurrence following neoadjuvant therapy

In one study of neoadjuvant chemotherapy, histology of wide excision specimens following downstaging revealed that in 16% of 227 cases there was evidence of multifocality of tumour, with the frequency greatest for larger tumours [23]. In a recent series of 25 patients, in whom breast-conservation surgery was performed after chemotherapy, in our own unit similar results were obtained: 6 cases revealed diffuse or multifocal disease in pathological examination, even though there was no palpable tumour in 5 of these patients.

In contrast to neoadjuvant chemotherapy, our experience with neoadjuvant endocrine therapy is that for most patients who respond (and become eligible for breast-conserving surgery), multifocality is not a problem, and complete excision is usually achieved. In a series of 65 patients who received tamoxifen, 45 had conservative surgery, and in only 1 case was there an incomplete excision (this was the patient with invasive lobular carcinoma in Fig. 1). In a subsequent series with aromatase inhibitors, 53 patients were suitable for breast conservation following treatment, and only 2 had an incomplete excision due to residual multifocal tumour. When the residual tumour is evaluated histologically, the nature of the response to neoadjuvant

Table 3
Median tumour volume reduction in series of patients with locally advanced breast cancer who received neoadjuvant endocrine therapy in the Edinburgh Breast Unit[a]

Agent	Number of patients	Patients with >50% reduction, *n* (%)	Patients with <50% reduction or <25% increase, *n* (%)	Patients with >25% increase, *n* (%)
Tamoxifen	65	30 (46)	34 (52)	1 (2)
Letrozole	36	32 (89)	3 (8)	1 (3)
Anastrozole	23	18 (78)	5 (22)	0
Exemestane	12	10 (83)	2 (17)	0

[a] Tumour volume changes (reduction or increase) were assessed by ultrasound measurements during the 3-month treatment period.

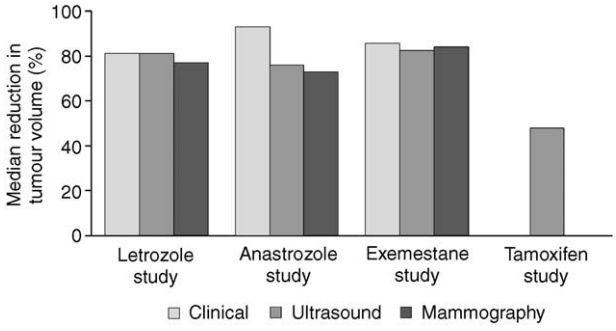

Fig. 4. Median reductions in clinical, mammographic, and ultrasound volume for patients who received neoadjuvant letrozole ($n=24$), anastrozole ($n=23$), or exemestane ($n=12$). For comparison, ultrasound response is shown for a series of patients treated with tamoxifen ($n=64$).

endocrine therapy appears to be somewhat different from the response to chemotherapy. Our impression is that after endocrine therapy the whole tumour seems to shrink concentrically, whereas with chemotherapy the extent of disease can sometimes remain similar while the cellularity of the tumour is markedly reduced.

Several studies have examined rates of tumour recurrence following neoadjuvant therapy and surgery (and in some cases local radiation therapy). Veronesi and colleagues reported 12 cases of local recurrence in 203 patients (5% incidence) at a mean follow-up of 3 years after preoperative chemotherapy followed by quadrantectomy and local radiotherapy [23]. This was considerably better than the 22% recurrence rate among comparable patients who underwent mastectomy. In another trial, recurrence rates were similar for patients receiving chemoendocrine therapy preoperatively and for those receiving only adjuvant treatment (3.5 and 2.7%, respectively, at 48 months' median follow-up) [24]. The importance of surgically removing tumours following complete responses to treatment is emphasised by a report that the rate of recurrence was significantly higher for *complete* responders who then received radiotherapy without surgery, as compared with *partial* responders who had surgery and radiotherapy [25].

There are no reported data on local recurrence after breast-conserving surgery in large numbers of patients following neoadjuvant endocrine therapy. Table 5 shows local recurrences in the series of patients treated in Edinburgh, with a distinction made between use of surgery alone versus surgery plus radiotherapy following preoperative treatment. While the overall recurrence rate without radiotherapy was 12%, only 1 patient (1.3%) had recurrence after surgery and radiotherapy. These results indicate that breast-conserving surgery

Table 4
Patients with locally advanced breast cancer requiring mastectomy before and after neoadjuvant endocrine therapy, in studies done at the Edinburgh Breast Unit

Agent	Number of patients	Number initially requiring mastectomy	Number requiring mastectomy after treatment	Conversion rate (%)[a]
Tamoxifen	65	41	15	63
Letrozole	36	24	2	93
Anastrozole	24[b]	19	2	89
Exemestane	12	10	2	80

[a] Percentage of patients initially considered only for mastectomy who underwent breast-conserving surgery following treatment.
[b] Includes one patient who did not complete full treatment.

Table 5
Local recurrences after neoadjuvant endocrine therapy followed by surgery with or without radiotherapy, in series of breast cancer patients at the Edinburgh Breast Unit

Agent	Number of patients	Number with no XRT[a]	Number with local recurrence	Number with XRT[b]	Number with local recurrence	Median follow-up (months)
Tamoxifen	43	13	2	30	0	78
Letrozole	33	12	2	21	0	61
Anastrozole	22	1	0	21	1	37
Exemestane	10	3	0	7	0	24
Total	108	29	4	79	1	48

[a] Number of patients who, following 3 months of neoadjuvant therapy, underwent breast-conserving surgery without local radiation therapy (XRT).
[b] Number of patients who, following neoadjuvant therapy, underwent both breast-conserving surgery and local radiotherapy.

followed by radiotherapy in responding patients achieves satisfactory local disease control.

8. Conclusions

Neoadjuvant hormonal therapy of ER+ and/or PgR+ locally advanced breast cancer is an effective and safe alternative to chemotherapy to downstage tumours for complete surgical excision or more conservative surgery. A randomised trial has demonstrated that the incidence and degree of downstaging are greater with the aromatase inhibitor letrozole than with the oestrogen receptor antagonist tamoxifen. This difference may be accounted for both by tumours with lower levels of ER expression (Allred scores <6) being more susceptible to letrozole, as well as by a higher rate of response in ER-rich (Allred score $\geqslant 6$) tumours. With appropriate patient selection based on criteria for ER-rich primary tumours and other favourable prognostic factors, neoadjuvant hormonal therapy may contribute to improved patient management.

Tumour response to neoadjuvant endocrine therapy should be evaluated by clinical examination together with either ultrasound or another imaging procedure, and at least a partial response ($\geqslant 50\%$ reduction in bidimensional measurements) occurs in over half of patients within 3 months. Complete tumour excisions are more likely to result from hormonal treatment than from chemotherapy, due to more concentric tumour shrinkage that minimises the occurrence of multifocal residual tumour. The incidence of local tumour recurrences is satisfactory following local excision and radiotherapy after neoadjuvant endocrine treatment.

Acknowledgements

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