The increased use of mammography and introduction of breast screening programmes have resulted in a rise in clinically-occult breast cancer, with one-third of all breast carcinomata diagnosed being non-palpable. These types of cancer have a unique natural history and biology compared to symptomatic breast cancer and this needs to be taken into account when considering surgery and adjuvant treatment. The majority of studies demonstrating efficacy of adjuvant treatments are largely based on patients with symptomatic breast cancer. The current evidence for the role of surgery and adjuvant therapy for screen-detected breast cancer was reviewed in light of their improved prognosis, compared to symptomatic breast cancer.

The increased use of mammography and introduction of breast screening programmes has resulted in an increase in the diagnosis of early breast cancer (1). Cancer detected by screening would be expected to require less treatment because it is diagnosed at an earlier stage. The Swedish Two Counties Trial demonstrated that patients with small node-negative cancer detected by screening had a mean 10% improved survival at 15 years compared to those with symptomatic node-negative tumors of similar size (2). This was reiterated by a Finnish cancer registry study, which identified that patients with screen-detected non-palpable T1 tumors have improved cancer-specific survival compared to those with symptomatic T1 tumours. It has also been shown that patients with screen-detected cancer have an improved overall survival and reduced breast, axillary and distant recurrence rate when compared to those with non-screen detected cancer (3). These findings suggest that there is an inherent biological difference between cancers detected by mammographic screening compared to those presenting symptomatically (4). Despite these differences, current protocols for adjuvant therapy do not take into account the favourable prognostic outcomes associated with screen-detected breast carcinomata when planning their management. The evidence for adjuvant therapies of screen-detected breast cancer was reviewed to determine if they should be treated like symptomatic cancer or if the screen-detected population should be considered as a distinct subset when considering their multidisciplinary management, including surgery, adjuvant radiotherapy, chemotherapy (including herceptin) and endocrine treatment.

**Surgery**

For symptomatic cancer, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 trial demonstrated that surgery without adjuvant therapy can cure 57% of patients with a clinically-negative axilla, at 10 years’ follow-up (5). The survival of patients with screen-detected cancer at 15 years’ follow-up has been shown to exceed 90% (6). The NSABP B04 trial also demonstrated that routine axillary clearance does not improve survival (5). Lack of survival benefit for axillary clearance was also demonstrated in the American College of Surgeons Oncology Group (ACOSOG) Z011 trial for patients with involved sentinel nodes, as long as they received adjuvant systemic therapy (7). The challenge we face with respect to screen-detected cancer is to provide patients with sufficiently adequate surgery to obviate the need for systemic therapy. It is likely, therefore, that the minimum requirement will remain wide local excision with sentinel node biopsy for the majority of patients. In the future, percutaneous excision and local ablative techniques are likely to become a viable alternative treatment for some of these tumours, although at present, these remain areas of clinical research interest.

**Adjuvant Radiotherapy**

Previous studies have demonstrated a reduction in local recurrence using breast radiotherapy after breast-conserving
surgery (5, 8-14). The proportions of screen-detected cancer in these studies ranges from 4% (8) to 76% (11). The study by Malmstrom et al. compared patients with stage I-II lymph node-negative breast cancer, undergoing standardised breast conserving surgery (10). Patients were randomised to postoperative radiotherapy or no further local treatment after breast-conserving surgery. In their study, 65% of included patients had screen-detected lesions. They found that the risk of ipsilateral breast recurrence was lower for screen-detected compared with clinically-detected breast cancer (Relative Risk (RR)=0.62, 95% Confidence Interval (CI)=0.42-0.91, \( p=0.015 \)). Amongst non-irradiated patients, the 5-year breast recurrence cumulative incidence was 11% (95% CI=8-16%) and 19% (95% CI=12-30%) in women undergoing screening and those with clinically detected lesions, respectively. The corresponding figures for the irradiated patients were 4% (95% CI=2.7%) and 5% (95% CI=3-10%), respectively. There was a highly significant difference comparing all four groups (\( p<0.001 \)). They found that the lowest risk in non-irradiated patients was for women greater than 49 years of age whose tumors were identified on screening. The cumulative incidence rate at five years was 10%. The Uppsala Breast Cancer Study randomised patients with tumors less than 20 mm, who underwent breast-conserving surgery and axillary clearance, to either postoperative radiotherapy or no adjuvant treatment and was composed of 45% screen-detected cases (12). Point estimates for recurrence rates at five years were 2.9% and 10.2% for the radiotherapy- and no-adjuvant treatment arms, respectively. Holli et al. (9) in their study of breast conserving surgery with and without adjuvant radiotherapy did not specify the numbers of screen-detected breast cancers. However, criteria for inclusion were lesions less than 20 mm and 40% of breast cancers were less than 10 mm. They found that the 5-year loco-regional disease-free survival was 93.7% and 85.9%, for the radiotherapy and no further treatment groups respectively. Schnitt et al. identified patients at low risk of recurrence who underwent breast-conserving surgery and could be spared adjuvant radiotherapy (11). In this study, 76% of the population were composed of screen-detected breast carcinomata. A total of 87 patients were enrolled before the trial was prematurely closed because the pre-defined stopping boundary of the sixth local recurrence had been crossed. At 56 months' follow-up, the recurrence rate was 16%, with a mean local recurrence rate of 3.6%. No single study demonstrated a significant overall survival advantage for adjuvant radiotherapy following breast-conserving surgery (5, 8-14). However, a benefit was demonstrated in the Early Breast Cancer Trialist’s Collaborative Group (EBCTCG) overview in which there was a significant reduction in not only local recurrence rates, but also in overall mortality in patients receiving adjuvant radiotherapy after breast-conserving surgery (15).

Adjuvant radiotherapy is essential for local control following breast-conserving surgery, even for small breast carcinomata, which would be considered as low risk for recurrence. Even in the study by Schnitt et al., which included over three-quarters screen-detected breast carcinomata, this was the case (11). This suggests that in patients with screen-detected breast cancer, adjuvant radiotherapy should generally be offered after breast-conserving surgery. However, studies have suggested that endocrine therapy may play a role in reducing the need for radiotherapy within excellent prognostic groups (16, 17) and the benefits of adjuvant radiotherapy should be discussed with patients taking into account their age and estimated benefit from endocrine.

The Role of Radiotherapy and Endocrine Therapy

Endocrine therapy has been demonstrated to increase overall and disease-free survival in patients with oestrogen-receptor positive (ER+) breast cancer after conserving and non-breast-conserving surgery (18, 19). NSABP-14 was a randomised, double-blind, placebo-controlled trial of adjuvant tamoxifen in 2,644 patients with node-negative and ER+ breast cancer (19). Over 57% of patients had tumours smaller than 2 cm and 38% of patients underwent breast-conserving surgery and radiotherapy, in both trial arms. NSABP-14 demonstrated that there was a significant difference (\( p<0.00001 \)) between the treatment groups in disease-free survival in favour of patients receiving tamoxifen (83% vs. 77%) at four years’ follow-up (19). Tamoxifen therapy also significantly reduced the rates of local and distant recurrence. The EBCTCG performed a meta-analysis of 37,000 women from 55 randomised trials of tamoxifen versus no-tamoxifen before disease recurrence (18). They identified that the proportional recurrence reductions at one, two and five years were 21%, 29% and 47%, respectively, with a significant trend towards greater effect with longer treatment. The proportional mortality reductions were 12%, 17% and 26%, respectively, demonstrating a significant trend in favour of tamoxifen use. The absolute reduction in recurrence was greater during the first five years, whereas improvement in survival grew steadily larger throughout the first 10 years. The proportional mortality reductions were similar for women with node-positive and node-negative disease, but the absolute mortality reductions were greater in women with node-negative disease. In the trials of five years of adjuvant tamoxifen, the absolute improvements in 10-year survival were 10.9% for node-positive (61.4% vs. 50.5% survival, \( p<0.00001 \)) and 5.6% for node-negative (78.9% vs. 73.3% survival, \( p<0.00001 \)) cases. The incidence of endometrial cancer approximately doubled in trials of one or two years of tamoxifen and approximately quadrupled in trials of five years of tamoxifen therapy.
The British Association of Surgical Oncology (BASO) II study evaluated the benefit of adjuvant radiotherapy and tamoxifen in patients with node-negative, small breast cancer (<20 mm) after breast-conserving surgery (16). All patients were over 70 years of age with clear margins, node-negative disease, but ER status was not identified. Randomisation of 1,171 patients was by radiotherapy versus no-radiotherapy, tamoxifen versus no-tamoxifen and a 2×2 randomisation of no tamoxifen, no radiotherapy; radiotherapy only; tamoxifen only; radiotherapy and tamoxifen groups. BASO II demonstrated that patients receiving both tamoxifen and radiotherapy had a significantly reduced local recurrence rate (p<0.001), with 15 out of 95 patients receiving neither treatment developing local recurrence (16). However, the local recurrence in the latter group was relatively low (1.9% per year) and this was reduced to 0.8% with the addition of tamoxifen. Tamoxifen had a significant protective effect after adjustment for radiotherapy (p=0.003) and vice versa (p=0.002). Receipt of both therapies conferred a significantly lower risk of local recurrence than radiotherapy alone (p=0.01) and also had a significantly lower risk than use of tamoxifen alone (p=0.006). However, the authors concluded that radiotherapy could be omitted for tamoxifen-alone in selected patients who fall into the Nottingham Prognostic Index (NPI) Excellent Prognostic Group (16). This Excellent Prognostic Group accounts for 15% of all invasive breast cancers and therefore hormonal therapy in place of radiotherapy following wide local excision for primary breast cancer could provide considerable savings whilst not-compromising clinical outcomes (16). Similarly, the Post-operative Radiotherapy in Minimum-risk Elderly (PRIME) II Trial recently reported that radiotherapy can be omitted in women over 65 years of age as long as they receive adjuvant endocrine therapy (17). In view of the very low recurrence rates, BASO II (16) and PRIME II (17) trials suggest that radiotherapy can be safely omitted in selected older patients with very small screen-detected tumours, particularly if they have comorbidities. NSABP-21 also attempted to assess the need for breast irradiation after breast-conserving surgery in patients with invasive breast cancer <10 mm comparing it to tamoxifen alone (20). Over one-third of patients had an unknown ER status. After breast-conserving surgery, 1,009 women were randomized to tamoxifen (n=336), radiotherapy and placebo (n=336), or tamoxifen and radiotherapy (n=337). At 8-year follow-up, the ipsilateral breast recurrence rate was 13.5%, 6.9% and 2.7% for tamoxifen, radiotherapy and placebo and radiotherapy and tamoxifen groups, respectively, therefore significantly favouring the latter group (p=0.0001). NSABP-21 also identified that the contralateral breast cancer rate was significantly lower in the tamoxifen-only group (0.9%; p=0.03) compared to the radiotherapy- and -placebo group (4.2%) and radiotherapy- and -tamoxifen group (3%). No significant differences in adverse events potentially attributable to tamoxifen were identified between these groups.

BASO II (16) did not randomize patients according to their ER status, and NSABP-21 (20) had over one-third of patients with unknown ER status. But both BASO II and NSABP-21 demonstrated an improved disease-free survival in patients with small ER+ breast cancer who undergo combination therapy with tamoxifen and radiotherapy as opposed to either of these treatments alone. NSABP-21 demonstrated the potential of tamoxifen to reduce the incidence of contralateral breast cancer when used alone and in combination with radiotherapy (20). The lower rate of contralateral breast cancer in the tamoxifen-only group of 0.9% compared to the irradiation-only group (4.2%) and combination therapy group (3%) is likely explained by the potential of radiotherapy to induce malignancy in the contralateral breast. This may suggest that prognostically-good patients could benefit from a more localized administration of radiotherapy in order to minimize this potential risk of contralateral breast malignancy and therefore optimise their therapy further.

Intraoperative radiotherapy has been used in the adjuvant treatment of breast-conserving surgery. The Targeted Intraoperative Radiotherapy-A (TARGIT-A) trial for Breast Cancer randomized a total of 1,721 women, undergoing breast-conserving surgery to intraoperative radiotherapy and 1,730 to external-beam radiotherapy (21). The 5-year risk for local recurrence was 3.3% (95% CI=2.1-5.1) for intraoperative radiotherapy and 1.3% (95% CI=0.7-2.5) for external-beam radiotherapy (p=0.042) with a median follow-up of 2 years and 5 months. The Electron Intra-operative Radiotherapy (ELIOT) trial of 1,305 patients randomized to intra-operative radiotherapy or external beam radiotherapy in breast-conserving surgery found that the 5-year local recurrence rate was 4.4% (95% CI=2.7-6.1) for intraoperative radiotherapy versus 4.0% (95% CI=0.0-1.0) in the external beam radiotherapy group (hazard ratio=9.3, 95% CI=3.3-26.3) (22). Both TARGIT-A (21) and ELIOT (22) did not demonstrate a significant difference in overall survival between the treatment groups. They did identify significantly reduced skin complications within the intraoperative radiotherapy group. The ELIOT trial demonstrated that poor prognostic factors, such as pathological size >2 cm, grade 3 malignancies, ER−, triple-negative and high proliferative index, could significantly predict for recurrence (22). Therefore, whilst intraoperative radiotherapy may not be suited for all patients, those with screen-detected cancer with good prognostic outcomes could benefit from this treatment modality in order to allow for safe oncological management and also avoid the inconvenience and recognised side-effects of externa-beam radiotherapy.
The Role of Adjuvant Chemotherapy

The purpose of adjuvant systemic therapies is to improve disease-free and overall survival rates associated with treatment of breast cancer by local therapies. It has been demonstrated that patients with screen-detected breast cancer have better overall survival and reduced recurrence rates compared to those with tumors of similar size and node-negative symptomatic cancer (2, 3). However, therapy for screen-detected breast cancer is determined by evaluating the patient’s likely benefit from adjuvant systemic therapy using models that are based on symptomatic breast cancer (23).

The benefit of chemotherapy is proportional to the risk of recurrence but complications of chemotherapy, which include thrombosis, sepsis and occasionally death, occur in 1-3% of treated patients and complications increase with age (23). Late adverse health effects such as leukemia and cardiotoxicity occur in 1% of patients from 5-13 years onwards (24). The EBCTCG recommended adjuvant chemotherapy for women between 50 and 70 years of age with adverse prognostic factors based on a 10-20% relative reduction in cancer mortality (23). However, the reduction in absolute mortality with chemotherapy in post-menopausal women older than 50 years was 3-5%, remaining constant at 15 years. Unless an individual’s risk of death is greater than 10% at five years, a proportional reduction in mortality from chemotherapy use greater than 1% is not achievable. The morbidity from its administration will equal its benefit and only patients with breast cancer with an increased annual hazard rate for mortality of 10% or greater in the five years after diagnosis will benefit from chemotherapy (25). Bundred et al. retrospectively assessed 875 cases of screen-detected cancer, with 600 symptomatic cases, in women aged 50-65 years of age and prognostic factors were compared for mortality (25). The 10-year survival was 92.1% for screen-detected breast cancer compared to 77.6% for symptomatic cases. Those with screen-detected breast cancer had a reduced mortality (RR=0.42, 95% CI=0.31-0.57), independent of grade, node status and tumor size. Those with ER+ screen-detected breast cancer had a lower annual mortality rate (0.6%) compared with symptomatic (4.3%; 0.001) or ER− screen-detected breast cancer (1.8%) (25). The NPI was calculated and demonstrated better survival for each NPI group in the screen-detected cohort. Those with screen-detected breast cancer had a better prognosis despite less chemotherapy use in every NPI group (except the Excellent Prognostic Group) compared to those with symptomatic cancer. Cancer-specific survival in screen-detected breast cancer was the equivalent of one NPI group better than that for symptomatic cancer. In the moderate prognostic group 1, 26% of those with ER+ symptomatic cancer had chemotherapy but mortality at five years was 8%, whereas it was 2% in group of moderate prognosis group 1 screen-detected breast cancer despite only 9% receiving chemotherapy (p=0.001). Bundred et al. found that the proliferative index was lower in the screen-detected group across all NPI groups compared to symptomatic patients (p<0.001) (25). This led them to conclude that the lower mortality in screen-detected breast cancer compared to symptomatic cancer was due to this lower proliferative index and that the use of adjuvant chemotherapy was overtreatment for ER+ screen-detected breast cancer with Good Prognostic Group and Moderate Prognostic Group 1 NPI scores. The study by Bucchi et al. compared adjuvant systemic treatment of a Italian cohort of patients with screen-detected breast cancer with a symptomatic one (26). They found that screen-detected breast cancer which was node-negative was significantly less often treated according to the St. Gallen Breast Cancer guidelines (27). This would suggest that there is a pragmatic approach amongst clinicians treating screen-detected breast cancer who are concerned about overtreatment in this low-risk population and who omit adjuvant chemotherapy. Barth et al. also found that patients with screen-detected breast cancer were less likely to be treated with systemic therapy compared to symptomatic patients (28% vs. 56%; p<0.0001) (28). These findings were largely attributable to their study demonstrating significantly less node-positive disease and smaller median tumour size in the screen-detected group (28). In view of the better prognostic outcomes of matched screen-detected versus symptomatic breast cancer, it is important to ensure that adjuvant systemic therapy is appropriately selected to avoid overtreatment and potential side-effects (2, 3).

In this area, the use of molecular profiling could be of assistance in determining adjuvant chemotherapy for patients with screen-detected cancer. The 21-gene Oncotype DX (Genomic Health Inc, Redwood City, CA, USA) recurrence score assay (29) has been shown to quantify the risk of locoregional recurrence in patients with ER+ node-negative disease. By using molecular profiling, it may be possible to optimise adjuvant therapies without over-treatment. However, the studies on which quantification of Oncotype DX assay has been performed are those consisting of only symptomatic patients (19, 30). Therefore, the generalized applicability of this assay to the screen-detected population could be questioned. It would be prudent to ensure that future assay quantification takes place on a cohort comprised of screen-detected breast cancer in order to ensure further confidence with the results.

Conclusion

The introduction of breast screening programmes has resulted in an increase in the diagnosis of clinically occult non-palpable breast cancer. The standard surgical management consists of wide excision and sentinel node...
biopsy. The benefit of subsequent adjuvant treatment is largely based on studies conducted on patients with symptomatic breast cancer. This means that despite the better prognosis of this subset of patients, their adjuvant treatment is aligned with that of patients with symptomatic breast cancer. The consequence of this management is adjuvant over-treatment, with the risk of associated short- and long-term side-effects. Molecular profiling may offer future assistance in selecting adjuvant chemotherapy for patients with ER+ and node-negative disease. However, validation of data against a screen-detected population is required in order to more accurately determine likely benefit of adjuvant treatments. It is, therefore, essential that future studies report on the proportion of screen-detected patients and take into account the different natural history of screen-detected cancer to ensure the most appropriate treatment is administered without overtreatment.

Conflicts of Interest

The Authors have no disclosures to make concerning financial and personal relationships with other people or organizations that could inappropriately influence their work.

References


6 [http://www.ncin.org.uk/publications/data_briefings/improved_survival_for_screen_detected_breast_cancer]


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