Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer.

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Background

Ductal carcinoma-in-situ (or DCIS) was an uncommon entity before the introduction of mammographic screening (<5% of clinically detected lesions) but a common finding since its introduction (~20-30% mammographically detected lesions) (22).Paradoxically, while invasive Stage I and II breast cancers are now treated with breast conserving surgery and post-operative radiotherapy, the non-invasive malignant lesion (DCIS) historically has been treated with mastectomy. Although these results have been excellent(23), the desire to also treat this condition with smaller resections has led to some centres attempting more conservative approaches such as observation or radiotherapy after lumpectomy.Pathologists have demonstrated in mastectomy specimens that DCIS is often described as multicentric (32%[22] - 76%[24[), with multicentricity and focal invasion related to lesion size (>25mm)(22). Holland(25) however favoured sampling of a three dimensional DCIS "tree" as the explanation for multicentricity, finding only 1 of 82 cases with non-contiguous spread. More meticulous examination of operative specimens has led to the understanding that DCIS lesions are often larger than appreciated on mammogram or clinical examination.Histological subtype (comedo v non-comedo) has prognostic significance. Comedo DCIS is of a higher nuclear grade, more likely to be associated with microcalcification and microinvasion.(25) Fortunately nodal involvement in DCIS is rare; positive axillary lymph nodes probably reflect sampling error in the pathology.Previous experience in lumpectomy for DCIS has been gained in only small numbers of patients. Lagios treated 79 patients with histologically completely excised large DCIS lesions (>25mm) prospectively with local excision alone. At 5.7 years (median follow up) 10 patients (13%) had recurred, with half (6.5%) being invasive lesions. (26)Radiotherapy experience for DCIS is similarly small. Of 67 patients with DCIS treated at the Institut Curie, 7 (%4.7) recurred at 5 years, with 5 being invasive recurrences.(23)This report(27) from the National Surgical Adjuvant Breast and Bowel Project, known as NSABP-B17, describes the initial results of a trial comparing observation with adjuvant radiotherapy in a group of patients treated with lumpectomy.

Trial Summary

Fisher et al.*27* report a collaborative multi-institutional, prospective, randomised clinical trial comparing lumpectomy followed by observation with lumpectomy followed by radiotherapy after complete surgical excision of DCIS.The trial accrued 818 patients between October 1, 1985 and December 31, 1990. The study found a statistically significant reduction in 'event-free survival' (EFS) after complete excision followed by radiotherapy. This reduction was seen entirely in ipsilateral breast cancers, and most markedly in invasive ipsilateral cancers. There were no patient deaths from breast cancer.

Trial Design

Hypothesis

The proposed null hypothesis states that in women with completely excised DCIS, "adjuvant breast irradiation adds no advantage in terms of ipsilateral second malignancy rates".

Sample size and Statistical Power

The ability of a study to demonstrate a significant difference depends on both the magnitude of the real difference and the size of the sample studied. Small real differences can only be reliably demonstrated in large samples. The previous reliance on p values has been discouraged in favour of both confidence intervals, as a more accurate guide to significance(4), and the power of the intended study.The power of a study should be estimated prospectively (i.e., before the study begins accrual) based on the likely difference between the study arms. Usually the outcome in the "control" arm reflects that obtained by standard treatment and is previously quantified. The treatment arm outcome may be previously quantified (retrospective studies) or estimated by clinical relevance (e.g., "a decrease in disease recurrence at 5 years of 50%")(5,28).Neither the predetermined sample size nor the power of the study were described in this study. However, using the tables based on the method of Casagrande et al(29)., a randomised trial with 381 patients per arm would have 80% one-sided power at the p=0.05 level, where the lower failure rate is 5%, and is 5% lower than the other arm (i.e., has a 10% failure rate). This trial, with historical outcomes of 13% 5-year recurrence post-lumpectomy(22), 5% 5-year recurrence post-lumpectomy and adjuvant radiotherapy(23), and 818 accrued patients exceeds these criteria. This study has the power to detect the expected pre-trial differences.

Trial Conduct

Eligible Population

Eligibility criteria listed were adequate to ensure that the sample of women included had DCIS, a pathological diagnosis and adequate surgery performed before inclusion. The matter of pathological review will be discussed later.

Patient Selection

The trial includes a wide range of DCIS patients. In the past there have been reports of adverse prognostic clinical features, such a presentations of Paget's disease of the nipple, nipple discharge, large palpable lesions(22,23,26) which are not controlled by stratification (see below). A large number of patients had very small DCIS lesions (~43% were <1mm) of uncertain prognosis.The management of multicentricity is also not addressed, although the validity of this diagnostic category has been addressed by Holland et al.(25)16 patients were inappropriately included but nevertheless analysed.30***Patient Stratification***Patient stratification at randomisation is a method that controls the balance of known prognostic variables, and is particularly useful when an imbalance of prognostic factors would render analysis meaningless, and where combinations of prognostic factors may delineate at risk subsets. In this trial patients were stratified at randomisation for :

- age (49 and >49)
- axillary dissection (performed or not performed)
- tumour type (DCIS and DCIS/LCIS)
- method of detection (clinical and mammography)However other prognostic factors of known importance were not included, but appear to be evenly distributed :histopathological subtype (comedo and non-comedo)
- tumour size (<25mm and >25mm)
- clinical syndrome. (Paget's, nipple discharge)

Failure to include histological subtype (comedo/non-comedo) and tumour size as stratification factors is a glaring deficiency since these factors have prognostic significance. Any future subgroup analysis will therefore be suspect.

Patient Randomisation

The method was adequately referenced, and reliable.

Patient Exclusion

There were two groups of patients excluded. 24 patients from a Montreal institution were excluded as the result of a NSABP decision after irregularities in the procedures of one surgeon31. Only 4 patients were excluded for inadequate follow-up.**T**

reatment Description
Surgery

The 'gold standard' of therapy of mastectomy has not been compared by randomised prospective trial to lumpectomy alone or with adjuvant radiotherapy. Retrospective and prospective data has shown an increased rate of ipsilateral breast cancer recurrence with less than mastectomy(23,26,32). Given this lack of data, a trial arm treated with mastectomy should have been included to permit a comparison of overall survival rates.The method of complete excision is incompletely described, omitting specimen processing. Specimen orientation with radiography is now considered good surgical practice. The method of "lumpectomy" is not described here33, Some investigators have described complete excision as a variable procedure.(34)The process described in the report is inadequate to permit a surgeon to reproduce the surgical and pathological techniques used.

Radiotherapy

Radiotherapy details are sufficient to allow identical treatment and permit consistent reporting of dose.However the reasons for the use of a tumour volume boost in 9% of cases are not detailed. Since boosts would usually be applied in patients thought to be at risk of local recurrence (thus needing a higher dose), a confounding variable has been introduced.

Pathology

The method of pathological verification of excision margins is not detailed (frozen section or embedded specimens +/- inking), and the action of surgeons subsequently is also not described (number of re-excisions permitted to attain clear margins).Holland(25) has shown that multicentric lesions are uncommon, however for the purposes of this study, delineation of the pathological definition of singularity is required. Individual institutions provided the pathological diagnosis without central review, however the diagnosis of DCIS has already been shown to have a degree of inter- and intraobserver variation with respect to microinvasion and atypical ductal hyperplasia(32).A review panel of pathologists to maintain patient homogeneity and quality assurance of pathological processes is highly preferable in this study, since the appreciation of microinvasion is central to the raison d'etre of the study.

Such a panel increases a study's power(35).

Trial Analysis

Statistical Analysis

The statistical method used is the life-table estimate (Kaplan-Meier actuarial method)(36) to determine survival. The curves were compared with a two sided summary chi-square (log-rank) test(37). Other summary functions (average annual incidence rates, cumulative incidence rates, relative risks) were compared using the chi-square test.Statistical significance was determined by a p value of <0.05, and 95% confidence intervals were provided.The statistical analysis is suboptimal in the following aspects :

- given the null hypothesis that radiotherapy adds no advantage in terms of recurrence rates, event-free survival is not an adequate surrogate endpoint(38). Fortunately the other events are numerically evenly distributed; still the additional number of events will enhance attainment of statistical significance when the number of relevant endpoints is small.
- given the strong prior hypothesis that radiotherapy, as has been shown in early invasive carcinoma, would provide an advantage in 'endpoint' free survival, the use of a two sided test is another method of ensuring statistical significance. A one sided test is preferable for this study.
- The authors also tested for interactions with a univariate and multivariate proportional hazards analysis (method of Cox). This included stratification variables and treatment given. Unfortunately, important prognostic factors (size, comedo histology) have not been included, leaving the hazards analysis suspect.
- The more significant oversight revolves around the issue of prospective determination of study power (addressed above).
- annual evaluation of statistical significance is described. Frequent analyses is more likely to derive a false positive result. The details of data surveillance procedures should be provided along with methods to be utilised when statistical significance is attained.(7)

Confounding Variables

Although the patient group contains a homogeneous and well defined population with DCIS, the inadequate stratification for prognostic factors will compromise subset analysis with later publications.The exclusion of the Montreal patients may introduce a confounder, but given the small numbers this is unlikely. A later analysis of this effect is expected.The use of a boost to the excision site indicates that prognostic factors are determining alteration in treatment, this will confound the results. Fortunately this occurrence was not common.

Trial Outcome

Criteria for Evaluation

Endpoints

The patients were observed at well-defined clinically-relevant intervals for endpoints that included :

- recurrence of ipsilateral breast cancer (including DCIS, invasive breast cancer)
- occurrence of contralateral breast cancer
- regional metastasis
- distant metastasis
- second primary cancer
- patient death

The position and multicentricity of the recurrent lesions were noted and secondary treatment reported, however the rationale of secondary treatment was not detailed.In the analysis, the first event after treatment was used to define "event-free survival". This choice would produce optimistic results for two reasons :a. the study aimed to determine the effect of treatment in "preventing a second cancer in the ipsilateral breast", not event-free survival.b. in the randomised NSABP-B06 protocol, radiotherapy was shown to significantly increase the time to relapse without affecting overall survival.(38)The median follow-up time is only 42 months. Later analysis is likely to show an increased rate of local recurrence in both arms. The qualitative difference should remain and be more instructional.

Toxicity

There are no toxicity data reported, and this represents a major deficiency. Where the benefits of treatment are small, even slight toxicities may have significant impact on utility. In particular, where excisions have been small, the effects of radiotherapy on cosmesis should be meticulously detailed.

Protocol Violations

Only 2.5% of patients did not meet entry criteria, 4 patients had inadequate follow up, and 16 patients were later found not to meet inclusion criteria (microinvasion, positive margins, previous cancer history, delayed radiotherapy, advanced disease). This is an excellent rate of violations.

Exclusions

One group of patients were excluded from analysis. Patients with full data from Montreal were voluntarily excluded by the NSABP as the veracity of their data could not be verified. These reports, along with letters, appear in a later issue of the same journal(31,40). The same reports stated that interim analysis revealed no material differences in the results of any of their trials after exclusion. A more detailed report was promised.

Results

The analysis with a median follow-up of 42 months shows that :a. invasive ipsilateral breast cancers were reduced after radiotherapy (2.6% v 0.6%). This result was highly significant ($p<0.001$).b. recurrent ipsilateral DCIS cancers were reduced after radiotherapy (2.6% v 1.5%). This result was non-significant ($p = 0.055$)c. the rates of other end-points were not reduced after radiotherapy. (contralateral breast cancer, regional lymph node and metastatic disease, and second primary cancers)d. three patients died of breast cancer, but only one after relapsing in the treated breast.e. regional or metastatic progression was uncommon (0.7-0.8%)

Conclusion

Acknowledgment of deficiencies in quality control of pathology are given but the authors conclude that they are unlikely to affect conclusions. No data is provided on which to challenge this remark.The authors conclude that given the reduction in incidence of ipsilateral second cancers, adjuvant radiotherapy after complete local excision is more appropriate than lumpectomy alone. They use their data as justification for the disuse of mastectomy in the setting of 5.1% local relapse (invasive and DCIS) after lumpectomy.

OVERVIEW

Ethics

This trial demonstrates the need for consideration of relevant ethical problems.The trial does not provide evidence that impinges on indications for or results of mastectomy. Mastectomy in the DCIS setting is nearly universally successful curative treatment, and has been the gold standard treatment. Initial trials of experimental treatment ought to include the gold standard treatment as one arm.

If the previous Phase II data accumulated are approximately correct (as they have been in this trial), such a trial would show an advantage to mastectomy. The recommendation of such a trial would maintain mastectomy as the better treatment.The authors should address the ethics of offering a less successful alternative (lumpectomy) or a less successful alternative (lumpectomy with radiotherapy) with higher cost. The issue of cosmesis has a deciding role in invasive disease where alternative therapies have equivalent local control and survival rates. This is not the case with DCIS where local control rates are not equivalent.

Internal validity

The trial is well conducted apart from the problems of radiotherapy boosts and Montreal patients.

External validity

This trial report does not permit clinicians to direct therapy confidently. The major clinical issues that this randomised study could have delineated - namely how important are the size of DCIS lesion and the histopathological identity of the DCIS lesion (comedo) - are not addressed. Given a predominance of lesions <1mm, the option of expectant observation could have been well established by this study design. Strict quality control in pathology was essential to the veracity of their findings, but was lacking.

Although the effectiveness of radiotherapy after lumpectomy is clearly demonstrated, the absolute benefits of such a treatment policy are small and may be judged as too small to warrant routine adjuvant therapy. The missing data on toxicities of radiotherapy treatment are relevant to this judgment.Based on the present report of this study, where the risk of recurrence is very small after lumpectomy, and where the use of adjuvant radiotherapy is only likely to benefit 2-3% of women treated, I would recommend close surgical followup for those concerned with cosmesis and mastectomy for those concerned about maximizing their survival chances.