Combined chemotherapy and Radiotherapy for Patients with Breast Cancer and Extensive Nodal Involvement.

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STUDY DESIGN AND CONDUCT

Study Aim

The study aim was a retrospective review of a single institution's experience in the treatment of patients with non-metastatic breast cancer with extensive nodal disease (defined as having 10 or more involved nodes, or at least 70% nodal involvement if less than 10 nodes excised). All patients received radiotherapy and chemotherapy after mastectomy. The review was to examine survival, local control and freedom from distant failure.

The main problems with the stated objectives are that the use of tamoxifen in these patients is not mentioned, and that toxicity outcomes were not mentioned even though they are later discussed.

There is no mention of the use of historical controls as there is no actual control arm. In the discussion the current series is compared to previously published series with similar patient groups, although no formal statistical comparison is performed. This is a reasonable approach due to the difficulties in using historical controls in a statistical analysis, and this format allows readers to make up their own minds. However without a formal analysis, the authors need to be very careful about what is said regarding the "comparability" of the current series with those previously reported.

Sample size and power

No sample size was specified, and there was no statistical comparison with a control arm. The series reported is small, with only 64 patients included over a nine year period (1980-1988 inclusive). It is unclear as to why this time frame was chosen: was it due to long follow-up required, certain treatment regimes used over this time period, or were the results with these patients better than over other time frames. This is something that should be stated by the authors.

Patient selection

Source

There is no indication as to the source of patients, nor how patients were obtained. Were these patients referred by surgeons from outside the centre, or were they only from within: if from within, did all surgeons refer all patients for chemotherapy and radiotherapy. How thoroughly did the investigators attempt to obtain information regarding patients not referred: was there an attempt to go through hospital files, pathology department files, surgical files, chemotherapy files and radiation oncology files. What quality control measures were undertaken by the authors in this regard, and in other areas (such as histological verification).

Patient eligibility

Eligibility criteria include patients with non-metastatic breast cancer and extensive nodal involvement (as previously defined). The UICC staging system is referenced. Investigations performed to exclude metastases are described for all patients. As discussed above, it is unclear whether all patients with extensive nodal involvement were obtained for review: treatment with mastectomy, radiotherapy and chemotherapy is not a prerequisite for inclusion in this review.

Patients were excluded if they had significant cardiac or respiratory comorbidity (2 patients), or if they were 75 years of age or older (unknown number of patients). Number of patients excluded based on age should be stated.

It is unclear precisely what these patients were excluded from. Were they referred for consideration of adjuvant therapy but refused treatment based on these criteria at the time, or were they actually treated but not included in the retrospective series. This needs to be made clear. Furthermore, this retrospective review now only includes fitter, younger patients, and may be a review of only patients treated with surgery, chemotherapy and

Once again, quality control measures should be stated, including histological and investigation verification.

Treatment description

All patients had total mastectomy and axillary dissection. As has been noted, there is no indication whether surgery was performed by one or more surgeons. There is also no indication of the level of axillary dissection undertaken: one can only presume that this was variable due to the wide range of lymph node numbers excised. This should be stated.

The description of radiotherapy technique includes a "typical" scheme. However there is no indication of the range in doses, time schedules and fractionation received. There is no indication of how many patients had their internal mammary chain

(IMC) irradiated, only that it was not routine. These points should be clarified, as well as an indication of how many patients received planned treatment.

Chemotherapy schedules are fairly well documented, and numbers of patients receiving planned cycles and doses are discussed in the results. It is noted that there are several different schedules of chemotherapy used over the time period, which will be further discussed.

The use of tamoxifen is not well documented: there is no indication how many patients received tamoxifen, how many completed the planned course without dose reduction or cessation, or whether all oestrogen receptor positive patients received tamoxifen. These points should be clarified.

There is no indication of the variation in the overall treatment times for all planned chemotherapy and radiotherapy. This should be indicated by the authors.

Follow up

Patient follow-up procedures were well documented, and patients were followed up until June 1993 (although the article was not submitted until April 1994). There is a good length of follow-up. There is little indication of how follow-up data was obtained, whether all patients were followed up within the one institution, or how many different clinicians performed follow-ups. Ideally, each patient still living should have been seen within the unit by a single observer to document appropriate follow-up data. Some indication as to the manner of follow-up should be provided (the only mention is that toxicity data was collected from radiotherapy and chemotherapy records).

Two patients with metastatic disease were lost to follow-up, and will be discussed later.

Outcome measures

The outcome measures reported included:

- Overall local recurrence rate.
- Crude rate of freedom from distant relapse, and freedom from distant relapse by nodal grouping.
- Proportion free of distant relapse at 5 years.
- Proportion of patients surviving, and proportion surviving by nodal grouping.
- 5 and 10 year actuarial rate of freedom from distant relapse.
- 5 and 10 year overall survival rates.
- Number of patients alive and disease free for 8 years or more.
- Effect of age at diagnosis on the risk of distant relapse and survival.
- Percentage of patients with reduction of planned number of cycles of chemotherapy and dose reductions in each phase of chemotherapy.
- Percentage of patients suffering from specified toxicities: leukopenia, alopecia, moderate or severe arm oedema, desquamation, nausea and vomiting and pulmonary pneumonitis.

As has been mentioned, the desire to determine local control, freedom from distant failure and survival was discussed in the "purpose" section, however toxicity and dose intensity outcomes were not alluded to. These should be referred to in the prospectively determined study aims. There will be further discussion of the outcome measures chosen in the "analysis and results" section.

Treatment completion

Numbers of patients completing the various phases of chemotherapy are stated, although it is not clear how many patients completed all planned chemotherapy without dose reduction. Numbers completing planned radiotherapy and tamoxifen are not discussed, and should be stated.

Side effects

Toxicity data has been obtained by perusing radiotherapy and chemotherapy files: this method tends to under-represent side effects for many reasons. Often such data is not thoroughly recorded, patients may only report toxicities enquired about, and physicians may underreport and downstage toxicity. There does not appear to have been any attempt by the authors to specifically ask patients about toxicities encountered during treatment, to determine if this correlated with toxicities recorded.

There is also no attempt to provide a table of graded toxicities, which would also be very useful: however this depth of information is probably not available in a retrospective review. Interestingly, not all possible toxicities appear to have been assessed, including some very important ones. Non-specific side-effects such as DVT or PE, and specific side-effects such as breast cosmesis, telangiectasia, fibrosis, bone fracture, brachial plexopathy and thrombocytopaenia are some others that should have been assessed.

This information is relevant when discussing toxicity and should be incorporated in the results if possible.

ANALYSIS AND RESULTS

Patient characteristics

Several patient characteristics are discussed, including age and nodal category, Other important characteristics such as receptor status, menopausal status, tumour size and ECOG scores should have been considered. Also, a table with this information would have been very helpful. It is recognised that such information may not be available (another of the problems with a retrospective review). The division of patients by age, in order to account for menopausal status, is acceptable, though by no means ideal. This arbitrary division cannot accurately be extrapolated to menopausal group, however precise menopausal data was probably not available for this review.

Statistical analysis

The various statistical tests utilized are referenced by the authors. There are several points to be made about the statistical analysis in this review.

Firstly it is important to note that there is no attempt to statistically compare the current review with historical controls. In the discussion the authors provide a table of previous reports detailing treatment of patients with extensive nodal disease. This is used to make a basic comparison with the present review. Selected studies are also discussed in the text. This is a reasonable approach due to the difficulties inherent with a statistical analysis with the study design that the current authors use, however any comparisons made must be interpreted cautiously due to the many differences (both known and unknown) of the patients and their management.

A clear statement should be made as to which patients were included in the analysis, as previously stated in the "patient selection" section. The authors should also state which group the two patients lost to follow-up were included in. Both patients had metastatic disease, and in all likelihood have died.

The statistical analyses performed have utilized hypothesis testing rather than confidence intervals. The use of confidence intervals either alone or in addition to P values would be preferable, particularly when considering the small numbers in this review. The authors should provide confidence intervals. If the authors also wish to include P values, these should be stated, even when a result is "not significant", as in Tables 1 and 2.

The results as presented are difficult to interpret, and there is no clear breakdown of the overall results. I feel that a table describing numbers (and proportions) of patients alive and dead, as well as numbers in each group that failed, and where they failed, would be a great help. We are given the proportion of patients that failed locally, those free from distant failure, and overall survival, however we have no idea of patients who are alive and disease-free. The authors do give a figure of 45% disease-free survival in Table 8, however it is not certain whether this represents the 5-year actuarial rate of freedom from distant relapse. I believe that an analysis of disease-free survival should be provided, either in addition to, or instead of, freedom from distant failure.

It is also noted that in the "statistical methods" section of the paper, the authors describe the CBET test to be used for comparing differences in rates of local recurrence. However the authors have not actually compared or even referred to differences in local recurrence: they have only given a single figure of overall proportion of patients who recurred locally (12.5%). The authors should consider providing such a comparison, particularly since local control is an important aim of management in these patients. The small numbers involved in such a comparison would further support the use of confidence intervals.

When perusing Figure 1, it is noted that there are only 2 patients at risk for both 10 year rates of freedom from distant failure and overall survival. This should be noted in the text also for those readers who do not carefully study the figures.

It is noted that there is a serious error in Figures 2 and 3. The caption for Figure 2 is actually describing the curve in Figure 3, and vice versa. This must be corrected by the authors.

When analysing toxicity data, most figures given relate to chemotherapy side-effects. Surgery, radiotherapy and tamoxifen are all important parts of the treatment regimen, and all have significant toxicities, some of which have been previously discussed. The authors should provide figures relating to such toxicities. In addition, a table of graded toxicities should be provided if possible, as previously discussed. The authors should also indicate whether they believe full toxicity data was collected, or whether there is missing data. The authors state that there were no severe reactions to radiotherapy. I believe that this should be amended to say there were no severe acute reactions to radiotherapy, since severe arm oedema (a late reaction of radiotherapy and also a side-effect of surgery) was seen in 13% of patients.

Presentation

The errors with regard to Figures 2 and 3 require correction. More details of numbers of patients at risk should be provided for all curves. As mentioned, actual P values should be stated.

TRIAL CONCLUSIONS

The authors come to several main conclusions in the discussion section.

There were high rates of local control and moderate rates of freedom from distant relapse and survival using a protocol that is associated with acceptable toxicity and no treatment related mortality. Treatment was well tolerated regardless of menopausal status. The results are comparable to those of more recent studies using more intensive chemotherapy.

There was no significant difference in the risk of distant relapse or overall survival between the two nodal subgroups.

The majority of patients in the study developed local recurrence either concurrently or after distant relapse.

Randomized trials of bone-marrow transplantation for this subset of patients with extensive nodal disease should include a standard best-treatment arm in which patients are treated with adjuvant chemotherapy and radiotherapy similar to that used in our study.

As has been previously discussed, comparing the results of the current review with previous studies must be done cautiously. There are many problems that affect the ability to make such a comparison, including:

- the present review contains small patient numbers treated over a long time period
- there are multiple regimes of chemotherapy used in the present review, and an unknown number of patients also received tamoxifen
- the studies listed had different nodal categories (eg 8 or more nodes), and none used the criteria of 70% nodal involvement if less than 10 nodes
- some of the studies listed in Table 3 are from the 1970's and early 1980's
- there is no indication of the comparability of other studies in terms of design, patient selection, age, stage, prognostic factors, treatments received, follow-up, nor any other factors
- there is no indication of toxicities encountered in most of the other studies
- other problems with the current review as discussed (for example incomplete data regarding toxicity, lack of confidence intervals etc).

The comparison can still be made in the conclusion, however it would seem reasonable for the authors to acknowledge the inherent limitations of the current review, and of its comparison with those listed. I believe they should do so. This acknowledgement would not weaken their final conclusion: studies should include standard best-treatment control arms (ie that contain adjuvant chemotherapy and radiotherapy) in randomized trials of bone-marrow transplantation, in this high risk group.

The conclusion that "treatment was well tolerated regardless of menopausal status" should be amended to "treatment was well tolerated regardless of age grouping" , since an arbitrary cut-off of 50 does not necessarily indicate menopausal status.

The authors also need to consider the recommendations (discussed in the next section).

RECOMMENDATIONS

This review comes at a time when many trials of high-dose chemotherapy are being reported, and allows the authors to make some valid conclusions. I believe that it should be published, although I would have some recommendations for the authors to consider prior to publication:

- The use of tamoxifen should be mentioned in the "purpose" section as part of treatment
- Intended toxicity and dose intensity outcomes to be analysed should be mentioned in the trial purpose.
- The authors should state the reason for choosing the time frame analysed.
- The authors should clearly state the source of the patients.
- The authors should state whether all patients with extensive nodal involvement were referred for consideration of adjuvant therapy, and how this information was obtained.
- Total number of patients excluded due to age or comorbidity should be stated, as well as clarification of what they were excluded from (as discussed previously). The authors should state the effect of not including all patients on extrapolation of findings, particularly since patients excluded were older or had comorbidity.
- Quality control measures (such as histological confirmation and thoroughness of record searching) should be stated by the investigators.
- More information regarding surgical, radiotherapy and tamoxifen treatments should be given, as previously discussed, as well as an indication of the variation in overall treatment times.
- The authors should discuss how many patients received tamoxifen, how many completed the planned course without dose reduction or cessation, and whether all oestrogen receptor positive patients received tamoxifen.
- Numbers completing planned radiotherapy should be stated.

- Important characteristics such as receptor status, menopausal status, tumour size and ECOG scores should be considered, and included in a table. If this information is not available, then this should be stated.
- The authors should also state how the two patients with metastatic disease lost to follow-up were analysed.
- The authors should consider including a table describing numbers (and proportions) of patients alive and dead, as well as numbers in each group that failed, and where they failed.
- Confidence intervals should be incorporated in the statistical analysis, either instead of, or in addition to P values. If P values are to be used, they should be given, not just quoted as "not significant".
- An analysis of disease-free survival should be provided.
- The authors should consider a comparison of differences in rates of local recurrence, in terms of nodal grouping and age grouping.
- It should be noted in the text that there are only 2 patients at risk for both 10 year rates of freedom from distant failure and overall survival.
- Figures 2 and 3 must be corrected by the authors.
- More details of numbers of patients at risk should be provided for all curves.
- The authors should provide more figures relating to toxicities of surgery, radiotherapy and tamoxifen. In addition, a table of graded toxicities should be provided, if possible. Missing toxicity data should be discussed.
- The statement that there were no severe reactions to radiotherapy should be amended to say "there were no severe acute reactions to radiotherapy", since severe arm oedema (a late reaction due to both radiotherapy and surgery) was seen in 13% of patients.
- The conclusion that "treatment was well tolerated regardless of menopausal status" should be amended to "treatment was well tolerated regardless of age grouping" , since an arbitrary cut-off of 50 does not necessarily indicate menopausal status.
- In the discussion the authors should acknowledge the inherent problems in extrapolating results from this study, as well as the difficulties in comparing this review with other studies. They might also add that any comparisons made must be interpreted cautiously