Improvements in breast cancer survival over time, related to adjuvant treatment and node status

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Abstract

Background: There has been an increase in the use and effectiveness of adjuvant treatment for operable breast cancer and the aim of this study was to examine whether this has resulted in improved survival for all prognostic groups.

Methods: A retrospective study of 1517 patients with invasive breast cancer treated between 1980 and 2002 was carried out. The use of adjuvant treatment was compared between two time periods in patients based on nodal status, and survival was calculated by Kaplan–Meier life table analysis. Independent predictors for recurrence-free survival (RFS) were determined by Cox regression analysis.

Results: The use of adjuvant therapy increased for all prognostic groups. On multivariate analysis the use of radiotherapy and endocrine therapy was positively associated with RFS which was significant in the second time period. Outcome in node positive patients improved: five-year RFS from 59% to 76%, $p < 0.01$ and breast cancer specific survival (BCSS) from 70% to 83%, $p < 0.01$. However, there was no survival improvement in the larger group of node negative patients; BCSS 93% versus 95%, $p = 0.99$. Within the node negative group, patients with tumours ≥ 2 cm had an improved RFS from 80% to 88%, $p = 0.02$.

Conclusion: The increased use of adjuvant therapy was associated with an improved outcome in node positive patients. For node negative patients with good prognostic features the evidence of benefit was marginal.

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Keywords: Breast cancer survival; Lymph node status; Adjuvant treatment

Introduction

Breast cancer survival is improving[1] and studies have shown that use of adjuvant treatment is one of the main reasons. Chemotherapeutic drugs have become increasingly effective over the past decades and have produced a significant reduction in breast cancer mortality rates.[2,3] This, in turn, has led to a general rise in the use of systemic adjuvant therapies.[4] But, depending on stage of the disease and tumour characteristics, there has been debate about the indications for and absolute benefit from adjuvant treatment in different prognostic groups.

The present study examined two groups of patients, those who were node negative and those who were node positive at the time of diagnosis. The aim was to compare the use of adjuvant therapy between two time periods and to relate changes to differences in breast cancer recurrence and survival.

Methods

Patient selection

The study was a review of breast cancer patients diagnosed between 1980 and 2002. Patient details were collected prospectively on an actively managed database and the follow-up is near-complete. Only patients with operable breast cancer were included in the study and those who had no node status recorded, solely in situ carcinoma or bilateral disease were excluded.

Tumour characteristics and adjuvant treatment

The remaining 1517 patients were divided into two groups according to the nodal status at the time of diagnosis. The following data were compared for those with positive or

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negative nodes, between two time periods (1980–1995 and 1996–2002): median age, tumour type, tumour size, tumour grade, type of operation and the use of adjuvant chemotherapy, endocrine therapy and radiotherapy.

The adjuvant chemotherapy regime in patients diagnosed during the first time period consisted of combination therapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF). During the year of 1996 this was switched to the routine use of doxorubicin and cyclophosphamide (AC) when studies had confirmed the superiority of anthracycline combinations.

Statistical analysis

The results were analysed using the Chi-square and Mann–Whitney U test.

Time to first recurrence and length of survival were determined from the date of diagnosis until the date of recurrence or death or the last clinic date if no event had occurred. Data were included until July 2007. Median follow-up time was 140 months for patients diagnosed between 1980 and 1995 and 71 months for patients diagnosed between 1996 and 2002. The Kaplan–Meier method was used to calculate recurrence-free survival (RFS), breast cancer specific survival (BCSS) and overall survival (OS) and survival curves were compared using the log-rank test. Independent predictors for RFS were determined with Cox regression analysis. Differences were considered to be statistically significant at $p < 0.05$.

Results

Overall survival improvement

There was a significant improvement in RFS and BCSS when comparing the two time periods 1980–1995 and 1996–2002. RFS increased from 76% to 85% (HR 1.63, 95% CI 1.32–2.01, $p < 0.01$), and BCSS from 84% to 90% (HR 1.4, 95% CI 1.1–1.82, $p < 0.01$). Use of adjuvant therapy was significantly increased during the latter period, in both node positive and node negative patients including prognostic subgroups (Table 1). In Cox regression analysis the use of adjuvant radiotherapy and endocrine therapy were independent predictors for RFS irrespective of time period. In separate analyses use of radio- and endocrine treatment were significant in the second but not in the earlier time period (Table 2).

Survival in node positive disease

There was a higher proportion of infiltrating ductal carcinomas diagnosed during the earlier time period (88% versus 78%, $p < 0.01$; Table 3) but in general tumour characteristics for node positive patients were comparable between the two groups. Five-year RFS improved from 59% in the first to 76% in the second period (HR 1.92, 95% CI 1.46–2.53, $p < 0.01$; Fig. 1). Local RFS alone

Table 1
Use of adjuvant treatment in subgroups (Chi-square test)

	1980–1995	1996–2002	p-Value
Overall	758	759	
Radiotherapy	227	455	<0.01
Chemotherapy	145	236	<0.01
Endocrine therapy	561	675	<0.01
Node positive group	293	276	
Radiotherapy	68	180	<0.01
Chemotherapy	101	169	<0.01
Endocrine therapy	227	245	<0.01
Node negative group	465	483	
Radiotherapy	159	275	<0.01
Chemotherapy	44	67	0.03
Endocrine therapy	334	430	<0.01
Node negative tumours < 2 cm	210	275	
Radiotherapy	86	181	<0.01
Chemotherapy	14	26	0.27
Endocrine therapy	154	252	<0.01

increased from 84% to 95% (HR 2.97, 95% CI 1.74–5.25, $p < 0.01$). BCSS improved from 70% to 83% (HR 1.67, 95% CI 1.23–2.28, $p < 0.01$) and OS from 68% to 79% (HR 1.39, 95% CI 1.06–1.83, $p = 0.02$).

Survival in node negative disease

Node negative patients diagnosed during the second time period had on average smaller sized tumours (Table 3). BCSS and OS were similar in both time periods, BCSS 93% versus 95% (HR 1.0, 95% CI 0.65–1.53, $p = 0.99$) and OS 89% in both time periods (HR 0.85, 95% CI 0.64–1.15, $p = 0.3$).

Subgroup analysis of node negative patients by tumour size showed a significant difference in RFS for patients with tumours ≥ 2 cm. Five-year RFS was 80% for patients diagnosed during the first compared to 88% for patients diagnosed during the second time period (HR 1.72, 95% CI 1.11–2.7, $p = 0.02$; Fig. 2). There was no difference in RFS for patients with tumours < 2 cm in size (93% versus 91%, HR 0.82, 95% CI 0.47–1.41, $p = 0.46$; Fig. 3) and no difference in local RFS for this group (97% in both time periods, HR 1.07, 95% CI 0.44–2.63, $p = 0.88$). Subgroup analysis by tumour grade did not show any statistical difference in RFS for patients with Grade I tumours (95% in both periods, HR 1.29, 95% CI 0.58–2.98, $p = 0.53$) Grade II tumours (86% versus 91%, HR 1.23, 95% CI 0.73–2.07, $p = 0.44$) or Grade III tumours (82% versus 87%, HR 1.29, 95% CI 0.88–1.91, $p = 0.19$).

Discussion

Adjuvant treatment and survival in node positive patients

The present study shows that breast cancer recurrence rates and survival have significantly improved over time,