Eur J Cancer, Vol. 27, No. 9, pp. 1132–1137, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Breast-conserving Treatment or Mastectomy in Early Breast Cancer: a Clinical Decision Analysis with Special Reference to the Risk of Local Recurrence

Lia C.G. Verhoef, Lukas J.A. Stalpers, André L.M. Verbeek, Theo Wobbes and Willem A.J. van Daal

A clinical decision analysis was performed to judge the impact of local recurrences after breast-conserving treatment (BCT) on the (quality-adjusted) life expectancy of breast cancer patients. A life-long follow-up of two patient groups, one of which had undergone mastectomy and one BCT, was simulated by a Markov model of medical prognosis. Data used in the model originated from the literature. Since results in the source papers were not split according to stage, we performed two analyses: one with data from all source studies (T_1 and T_2) and one with data from source studies, concerning only T_1 patients. In both analyses, the conclusion was that BCT yields better quality-adjusted life expectancy than mastectomy. Sensitivity analysis, however, identified subgroups of patients who should preferably undergo mastectomy. These subgroups are: patients preferring mastectomy to BCT, patients with a high risk of local recurrence, young patients and patients at high age, if they also have a high local recurrence risk. For these groups, patient preferences should play a major role in recommending treatment.

Eur J Cancer, Vol. 27, No. 9, pp. 1132–1137, 1991.

INTRODUCTION

RANDOMISED TRIALS which employ modern radiotherapeutic and surgical treatment techniques do not show a difference in survival after mastectomy or breast-conserving treatment (BCT) for early breast cancer [1–11]. BCT thus seems to be the treatment of choice, since it yields the same survival and is less mutilating than mastectomy. However, after mastectomy, most local recurrences occur within the first 3 years after initial treatment, whereas after BCT the local recurrence risk remains stable during a follow-up of 15–20 years [1, 13]. Local recurrence rates up to 25% have been reported after 25 years of follow-up [14].

About 15% of local recurrences is irresectable and the patient will eventually die from the disease [1, 15–23]. The other patients can be treated by a salvage mastectomy and they have a good prognosis in comparison to patients who develop a local recurrence after mastectomy [24]. Thus, the higher local recurrence rate will not readily affect survival of the whole group treated by BCT. Only one study demonstrated impaired survival after local recurrence following BCT [25].

Apart from survival, it is important to balance the psychological impact of local recurrence and salvage mastectomy against the benefit of a preserved breast. We performed a clinical decision analysis in order to integrate information from randomised trials with data from retrospective series with a longer follow-up. In this way a balanced judgment about which therapy is to be preferred can be made.

Correspondence to L.C.G. Verhoef.
L.C.G. Verhoef, L.J.A. Stalpers and W.A.J. van Daal are at the Insitute for Radiotherapy; A.L.M. Verbeek is at the Department of Epidemiology; and T. Wobbes is at the Department of General Surgery, St. Radboud University Hospital, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
Received 11 Mar. 1991; accepted 7 June 1991.

METHODS

Definitions

A local recurrence is localised in the lumpectomy scar or in the ipsilateral breast. No distinction is made between a local recurrence and a second primary tumour. A regional recurrence is localised in the axilla, supraclavicular or parasternal nodes.

Literature search

Literature was obtained from the MEDLINE database, from regularly checking *Current Contents* and from references in papers and books. Inclusion criteria for papers were: results of randomised trials of total or radical mastectomy versus some form of tumorectomy with axillary dissection, followed by a radiation dose of at least 50 Gy to the tumour bed, reported according to the TNM classification and concerning $T_{1\text{-}2}N_{0\text{-}1}M_0$ patients. In order to estimate the local recurrence risk beyond the follow-up period of the trials, we searched for retrospective series, which were included in the analysis if they provided an actuarial follow-up of at least 15 years and provided separate local and regional recurrence rates. Because no series were available in which all patients had undergone axillary dissection, we included papers reporting the results of BCT without axillary dissection. The search yielded 234 papers, among which were 15 reports about 4 randomised trials [2–12, 26–29], and the rest were reviews, comments, and papers on retrospective series of breast cancer patients, treated by BCT. If we found more than one report about the same patient group, we utilised the report that provided the most detailed information.

One of the four trials [26–29] did not meet our criteria. After selection, references [1, 3, 4, 7, 13–23, 30] were used.

Model

We modeled a Markov process to describe the fate of patients undergoing either BCT or mastectomy [31]. The model is represented in Fig. 1. Five possible health outcomes or Markov

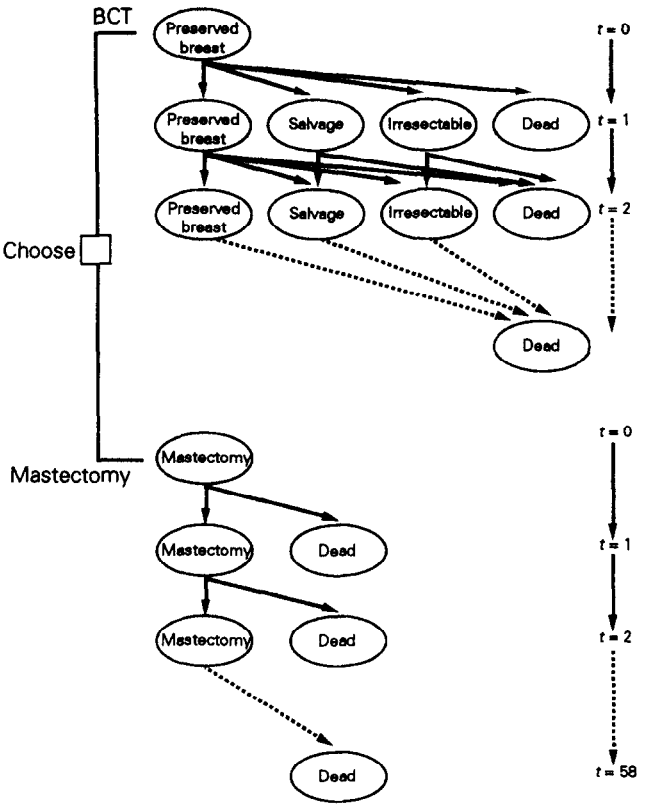

Fig. 1. Representation of the Markov model.

states were defined. Every year a patient can move from one state to another with a certain transition probability. After BCT, a patient will be in the state "preserved breast". She might develop a local recurrence, which will be treated by a salvage mastectomy (Markov state "salvage"). If the local recurrence is irresectable, the patient moves to the state "irresectable". From all states, it is possible to move to the final state "dead".

After mastectomy, patients will live in the state "mastectomy", until they move to the state "dead", either from their cancer or from age-specific mortality. Metastatic disease is not modelled in a separate Markov state, since the endpoints of interest are the occurrence of local recurrence and death.

The Markov model calculates the total amount of time that an individual is expected to spend in each health state after either treatment. Time spent in each Markov state is not of equal value. Every state is assigned a value between 0.00 and 1.00: a utility. A utility is referred to as a "ustate". The numerical value of a utility depends on its relative value among all possible health states. If Markov states are valued in this way, the resulting number is the expected number of quality adjusted life years (QALYs) [32]. In order to obtain the unadjusted life expectancy, all Markov states are assigned the value 1, except "udead", which equals 0.

Transition probabilities and utilities

For every transition probability, a baseline value was computed. For the actuarial survival curves published in the reports of the trials (Table 1) it is possible to estimate the overall mortality risk (*OMR*) in every particular year of follow-up. The yearly risks from three trials were combined to one value by computing mean yearly risks, weighted for the number of patients. After subtracting the age-specific and sex-specific mortality risk (*ASR*) [33] from these weighted mortality risks, the breast cancer specific mortality risk (*BCR*) results. Since the reported follow-up in the NSABP-trial was only 8 years, it was possible to compute a mortality risk for only this time. The *BCR* in the 9th year was assumed to equal the arithmetic mean of the risks in the preceding years, and to decrease linearly in the subsequent years to zero in the 30th year of follow-up. To compute the *OMR* for every plausible age at diagnosis after any period of follow-up, *OMR* was modelled as:

$$OMR_{(t)} = BCR_{(t)} + ASR_{(age\ +\ t)} \quad \{1\}$$

in which t is the time in years from the diagnosis, and *age* is age at diagnosis.

The yearly risk of local recurrence was computed by applying formula {2} to the weighted average of the 8-year local recurrence rates given in the trial reports:

$$\text{yearly risk} = 1 - [(1 - R)^{1/x}] \quad \{2\}$$

in which R is the cumulative risk at x years. The yearly risk in the 9th to 20th year of follow-up was calculated from the retrospective series by computing a weighted mean of the local recurrence risks at 20 years [1, 14, 15], and transforming this value into a yearly risk according to formula {1}. The local recurrence risk at 20 years as calculated by the model is lower than the risk reported by the retrospective series, because information of the older series with a higher risk was combined with the results of the newer trials, which reported a lower risk in the first years. We assumed that the yearly local recurrence risk beyond 20 years would linearly decrease to zero in the 25th year of follow-up.

The baseline values used in the analysis are estimates based on literature research. The baseline age at diagnosis is the weighted mean of the mean age at entry as reported in the papers. The baseline analysis is performed with these estimates. In order to account for the uncertainty of these estimates, the probabilities and utilities are varied between a low and a high estimate, the "plausible range". Thus, the sensitivity of the decision to variations over this range can be assessed [34]. The

Table 1. Characteristics of the trials

Study	Treatment options	*n*	TNM-classification	Mean age at entry	Actuarial follow-up (yrs)
Milan [8, 12]	Quadrantectomy, axillary dissection and irradiation	352	$T_1N_0M_0$	50.9	13
	Halsted mastectomy	349		50.1	
Gustave-Roussy [4, 6]	Tumorectomy, axillary dissection and irradiation	88	$T_1N_{0-1}M_0$	51.4	10
	Halsted mastectomy	91		51.8	
NSABP [2, 3]	Lumpectomy and axillary dissection*	636	$T_{1-2}N_{0-1}M_0$	51†	8
	Lumpectomy, axillary dissection and irradiation	629	(T_{max}, 4 cm)		
	Total mastectomy	590			

*This treatment arm was not considered in the analysis.
†Mean ages not given; this is an estimation.

low and high values that constitute the boundaries of the plausible ranges are computed by calculating a 95% confidence interval of the values found in the literature.

The utilities assigned to the health states and their plausible ranges are based on the utilities and their standard deviations as measured by De Haes *et al.* who performed a utility measurement among experts in the field of breast cancer [35] (Table 2).

In the model, the utilities were incorporated in such a way, that "upreserved breast" ≥ "umastectomy" ≥ "usalvage" ≥ "uirresectable" ≥ "udead". This was achieved by defining all utilities, except "udead", which always equals 0, in terms of differences between "upreserved breast" and the actual utility.

Future life-years were not discounted in the baseline analysis. In order to account for time preference, we examined the effects of different discount rates d in the sensitivity analysis. The utility of future life-years was divided by $(1 + d)^t$, where t is the elapsed time in years from the starting age [36, 37].

Grouping of studies according to stage

Because the Gustave-Roussy and the Milan trials consisted of T_1 patients, contrary to the NSABP study, in which nearly half of the patients were T_2 patients, we performed two separate analyses. One was based on the data from the Gustave-Roussy and the Milan trials and one on the data of all three trials. It is thus possible to explore a possible shift in effect between T_1 patients and a mixture of T_1 and T_2 patients.

All calculations were performed by the software package DecisionMaker 6.1.01 [38].

RESULTS

Baseline analyses

According to the baseline analysis, a 50-year-old woman with early breast cancer (T_1 or small T_2) has a life-expectancy of 20.92 years after mastectomy and of 21.31 years after BCT. In terms of QALYs, the model predicts 19.81 QALYs after mastectomy and 20.23 QALYs after BCT, a benefit of 0.42 QALYs for BCT.

Table 2. Baseline values with plausible range

Variable	Baseline value	Plausible range	
		Low	High
Age			
All trials	50.9*		
T_1 only	50.7*	25.0	100.0
Local recurrence risk at 20 years			
T_1 only	0.14	0.06	0.21
All trials	0.19	0.11	0.26
Proportion of operable relapses	0.86	0.60	1.00
Probability to survive 10 years after salvage	0.56	0.44	0.68
Probability to survive 5 years after inoperable relapse	0.13	0.00	0.26
Duration of breast cancer mortality risk	30	25	35
Duration of local recurrence risk	25	20	30
Discount rate	0.00	0.00	0.10
"upreserved breast"	0.96	0.82	1.00
"umastectomy"	0.95	0.77	0.96
"usalvage"	0.84	0.50	0.95
"uirresectable"	0.61	0.00	0.84

*Weighted mean for the number of patients.

Table 3. Effect of different local recurrence risks on life expectancy

	Mastectomy	Breast-conserving therapy		
		Low risk	Baseline risk	High risk
All trials	20.92	22.12	21.31	20.54
T_1 only	22.63	23.47	22.57	21.75

If we know that this woman has a T_1 tumour, we can estimate her prognosis more accurately: life expectancy is 22.63 years after mastectomy and 22.57 years after BCT, a loss of 0.06 life-years or 22 days. In terms of QALYs, however, she can expect 21.43 QALYs after mastectomy and 21.50 QALYs after BCT, a gain of 0.07 QALYs. The decision to perform BCT in this patient thus requires a tradeoff between quality of life and life quantity.

On the basis of our baseline analysis we predict that the "average" patient with a small breast tumour will prefer BCT to mastectomy.

Sensitivity analyses

In order to study the effect of different patient characteristics on the stability of the conclusions, various sensitivity analyses were performed.

The effects on life expectancy of different local recurrence risks after BCT are presented in Table 3. In both analyses, a high local recurrence risk results in a shorter life expectancy after BCT than after mastectomy.

It was not possible to define a simple plausible range for mortality risk, because these risks are different each year. Instead, threshold values for mortality risk were computed. The threshold value of mortality is the extra yearly risk of mortality that causes the preference to switch from BCT to mastectomy. For T_1 patients, the baseline analysis predicts a shorter life expectancy after BCT than after mastectomy. If the 10-year survival after BCT is augmented by 0.2%, or the 10-year survival after mastectomy lowered by 0.2%, the life expectancy after both treatments would be the same. The corresponding threshold values for both T_1 and T_2 patients are an extra 10-year survival after mastectomy of 1.2% and a diminished 10-year survival after BCT of 1.3%. This "lability" of preference is expected, since the baseline mortality risks are virtually equal, thus a small weight on one side of the balance can cause a switch from one side to the other.

In Table 4, the effects of varying different variables over their plausible ranges are displayed. Local recurrence risk, age, the proportion of operable relapses and the probability to survive 10 years after salvage, the durations of both local recurrence and breast cancer specific mortality risk, "upreserved breast" and "usalvage" can alter the decision.

Figure 2 illustrates the interaction of age with local recurrence risk, both for T_1 patients only and for all trials. The area above the curve represents ages at which, in combination with a certain local recurrence risk, mastectomy is preferred. This figure is based on quality-adjusted life expectancy. The combination of young age and higher local recurrence risk reinforces the preference for mastectomy. The different curves denote different values of "umastectomy". The lower the utility of mastectomy, the smaller the area that represents a preference for mastectomy. It is remarkable, that when "umastectomy" is

Table 4. Sensitivity analysis

Variable	Value		Benefit of BCT in QALYs: All trials	Benefit of BCT in QALYs: T_1 only
Age	25		−0.47	−1.13
	50		0.41	0.05
	75		0.25	0.20
	100		0.02	0.02
Local recurrence risk at 20 years†	0.11	0.06	1.31	1.04
	0.19*	0.14*	0.42	0.07
	0.26	0.21	−0.43	−0.84
Proportion of operable relapses	0.6		0.02	−0.23
	0.86*		0.42	0.07
	1.0		0.64	0.22
Probability to survive 10 years after salvage	0.44		0.12	−0.14
	0.56*		0.42	0.07
	0.68		0.77	0.31
Probability to survive 5 years after inoperable relapse	0.00		0.39	0.05
	0.13*		0.42	0.07
	0.26		0.44	0.08
Duration of breast cancer mortality risk	25		0.25	−0.03
	30 *		0.42	0.07
	35		0.54	0.14
Duration of local recurrence risk	20		0.54	0.15
	25 *		0.42	0.07
	30		0.35	−0.01
Discount rate	0.00*		0.42	0.07
	0.05		0.30	0.17
	0.10		0.21	0.15
"upreserved breast"	0.82		0.36	0.08
	0.96*		0.42	0.07
	1.00		0.44	0.06
"umastectomy"	0.77		3.79	3.83
	0.95*		0.42	0.07
	0.96		0.17	−0.21
"usalvage"	0.50		−0.17	−0.41
	0.84*		0.42	0.07
	0.95		0.61	0.21
"uirresectable"	0.00		0.39	0.04
	0.61*		0.42	0.07
	0.84		0.43	0.08

*Baseline value.
†First column denotes the risk for all trials, second column for T_1 patients only.

high, not only at young, but also at old age a threshold is found. Because local recurrence risk diminishes in time, the maximal gain from BCT is achieved after some time. The probability to move to states with low utility, like "salvage" or "irresectable" will have become very small, but the difference in utility between "umastectomy" and "upreserved breast" remains constant. At old age, life expectancy is short, and people will not reach this period of maximal gain from BCT. In Fig. 3, the relation between age at diagnosis, local recurrence risk and "usalvage" is displayed. For young age and high local recurrence risk the preference is very sensitive to diminishing "usalvage".

Some patients may, contrary to our assumptions, prefer mastectomy to BCT, because they feel safer when their breast is completely removed. We performed a threshold analysis with

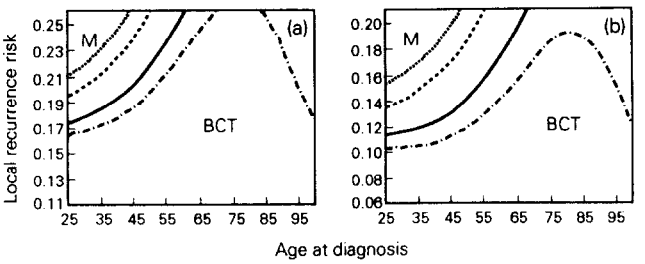

Fig. 2. Threshold analysis of quality-adjusted life expectancy for varying ages at diagnosis and local recurrence rates after breast conserving treatment (BCT) in the choice between mastectomy (M) and BCT. The lines denote combinations of age and recurrence risks for which the quality adjusted life expectancy are equal following BCT or M. Every line represents another value of "umastectomy": −·−·− "umastectomy" = 0.96, ----- = 0.92, ····· = 0.90. The solid line represents the baseline utility (0.95). (a) Analysis for all trials, (b) T_1 patients only. If a certain point, representing a combination of age and local recurrence risk is located below the line, BCT is the preferred treatment; if it is above the line, M is the preferred treatment.

"umastectomy" in which the condition "umastectomy" ≤ "upreserved breast" did not apply. If "umastectomy" equals 0.97 or more (at a baseline value of "upreserved breast" of 0.96), mastectomy is the preferred treatment for all trials. For the T_1 patients, mastectomy is the preferred treatment, when "umastectomy" equals 0.95 or more.

DISCUSSION

Treatment effects in patients with early breast cancer are difficult to evaluate because the time frame of the disease is very long. To predict the eventual effect of the primary treatment on survival, a life-long follow-up is needed, because of the prolonged risk of recurrence. With a Markov model, it is possible to simulate such a life-long follow-up. The value of the Markov analysis presented here is that we were able to highlight the effect of a factor that has caused concern: the continuous occurrence of local relapses after BCT during a long time.

In order to design a manageable model, we created only separate Markov states for health states, that were directly related to the questions posed. Possible side-effects of radiotherapy or complications of mastectomy were not incorporated in the analysis. Side-effects of radiotherapy, other than fibrosis of

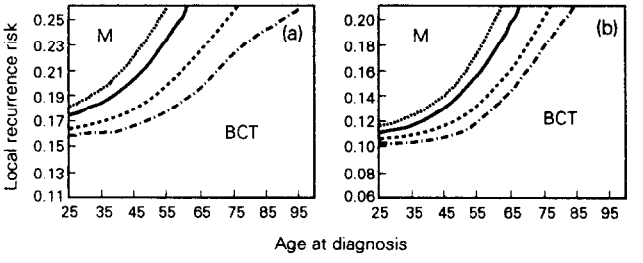

Fig. 3. Threshold analysis of quality-adjusted life expectancy for varying ages at diagnosis and local recurrence rates after breast conserving treatment (BCT) in the choice between mastectomy (M) and BCT. The lines denote combinations of age and recurrence risks for which the quality adjusted life expectancy are equal following BCT or M. Every line represents another value of "usalvage": ····· = 0.95, ----- 0.65, −·−·− = 0.50. The solid line represents the baseline utility (0.84). (a) Analysis for all trials. (b) T_1 patients only. If a certain point, representing a combination of age and local recurrence risk is located below the line, BCT is the preferred treatment;if it is above the line, M is the preferred treatment.

the breast, have become very rare with modern radiotherapeutic techniques. The main consequence of breast fibrosis is a poor cosmetic result. By assuming a lower utility value for life with preserved breast, it is possible to account for this possibility in the sensitivity analysis.

The occurrence of lymphoedema depends on the treatment of the axilla, which is essentially independent from the treatment of the breast. Thus, we cannot expect a difference between patients treated by mastectomy or by BCT in this respect.

Complications of mastectomy, such as seroma or complicated wound healing are, in the view of the time-frame of the analysis, considered negligible. Operative mortality after mastectomy is assumed to be equal to operative mortality after lumpectomy and irradiation.

A remarkable observation in the analysis is that conservative therapy is supported more strongly, when T_2 patients are included. This is entirely due to the study by Fisher *et al.*, who observed a (non-significant) gain in survival after BCT, as compared to mastectomy [3]. Since the model copies the published survival curves exactly, this gain in life-expectancy is reproduced, and results in a stabler preference for breast conserving therapy. We did not find an explanation for this observation in Fisher's report. It might be due to a random variation in treatment outcomes, and the gain in life expectancy of lumpectomy and irradiation compared to mastectomy may well vanish when the follow-up becomes longer.

The differences found in the analysis were usually small and the choice between mastectomy and BCT can be characterised as a toss-up [39]. Because of its less mutilating character, BCT is to be preferred to mastectomy.

However, we identified some subgroups of patients who are possibly better off with a mastectomy. These patients are: (1) those who prefer mastectomy to BCT; (2) patients with a high local recurrence risk; (3) young women. In these patients conservative therapy can eventually result in a shorter (quality-adjusted) life expectancy because they are at risk for a very long time. If a young patient also has a high local recurrence risk, mastectomy deserves serious consideration; and (4) women of old age with a high local recurrence risk. Their life-expectancy is too short to accrue enough extra QALYs from the preserved breast to compensate for the shorter life-expectancy and the loss of utility associated with local recurrence.

We did not specify what constitutes a high local recurrence risk; many prognostic factors have been mentioned in the literature of which extensive ductal carcinoma *in situ*, involved resections margins and invasion of lymphatic vessels are the most prominent. Young age may also be an indicator of a higher than average local recurrence risk [40–42]. In interpreting the results of this analysis, the clinician should use his/her clinical judgment of which patient has a low, moderate or high local recurrence risk, taking into account the treatment results in his/her own hospital.

We believe that it is an important observation that even when a life-long follow-up is simulated, both treatments yield a virtually equal life expectancy at a baseline local recurrence risk of 14% for T_1 patients and 19% for both T_1 and T_2 patients. This risk is partially based on the results of older series and evidence cumulates, that with newer treatment techniques and sufficient radiation doses the local recurrence risk will be lower for patients treated nowadays [3, 4, 12]. However, we also showed, that a high local recurrence rate is able to affect survival, thus emphasising the importance of maintaining a good local control rate.

1. Kurtz JM, Amalric R, Brandone H, *et al.* Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course and prognosis. *Cancer* 1989, **63**, 1912–1917.
2. Fisher B, Bauer M, Margolese R, *et al.* Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985, **312**, 665–673.
3. Fisher B, Redmond C, Poisson R, *et al.* Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989, **320**, 822–828.
4. Sarrazin D, Lê MG, Arriagada R, *et al.* Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol* 1989, **14**, 177–184.
5. Sarrazin D, Lê MG, Fontaine MF, Arriagada R. Conservative therapy versus mastectomy in T1 or small T2 breast cancer—A randomized clinical trial. In: Harris JR, Hellman S, Silen W, eds. *Conservative Treatment of Breast Cancer*. Philadelphia, Lippincott, 1983, 101–111.
6. Sarrazin D, Lê MG, Rouesse J, *et al.* Conservative treatment versus mastectomy in breast cancer tumors with macroscipic diameter of 20 millimeter or less. *Cancer* 1984, **53**, 1209–1213.
7. Veronesi U, Banfi A, Del Vecchio M, *et al.* Comparison of Halsted mastetomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: long-term results. *Eur J Cancer Clin Oncol* 1986, **22**, 1085–1089.
8. Veronesi U, Del Vecchio M, Greco M, *et al.* Results of quadrantectomy, axillary dissection, and radiotherapy (QUART) in T1N0 patients. In: Harris JR, Hellman S, Silen W, eds. *Conservative Management of Breast Cancer*. Philadelphia, Lippincott, 1983, 91–99.
9. Veronesi U, Saccozzi R, Del Vecchio M, *et al.* Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981, **305**, 6–11.
10. Veronesi U, Zucali R, Del Vecchio M. Conservative treatment of breast cancer with the Qu.A.R.T. technique. *World J Surg* 1985, **9**, 676–681.
11. Veronesi U, Zucali R, Luini A. Local control and survival in early breast cancer. The Milan trial. *Int J Radiat Oncol Biol Phys* 1986, **12**, 717–720.
12. Veronesi U, Banfi A, Salvadori B, *et al.* Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomized trial. *Eur J Cancer* 1990, **26**, 668–670.
13. Harris JR, Recht A, Amalric R, *et al.* Time course and prognosis of local recurrence following primary radiation therapy for early breast cancer. *J Clin Oncol* 1984, **2**, 37–41.
14. Osborne MP, Ormiston N, Harmer CL, McKinna JA, Baker J, Greening P. Breast conservation in the treatment of early breast cancer. A 20-year follow-up. *Cancer* 1984, **53**, 349–355.
15. Fourquet A, Campana F, Zafrani B, *et al.* Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. *Int J Radiat Oncol Biol Phys* 1989, **17**, 719–725.
16. Calle R, Vilcoq JR, Pilleron JP, *et al.* Conservative treatment of operable breast carcinoma by irradiation with or without limited surgery—ten-year results. In: Harris JR, Hellman S, Silen W, eds. *Conserative Management of Breast Cancer*. Philadelphia, Lippincott, 1983, 3–9.
17. Barr LC, Brunt AM, Goodman AG, Phillips RH, Ellis H. Uncontrolled local recurrence after treatment of breast cancer with breast conservation. *Cancer* 1989, **64**, 1203–1207.
18. Haffty BC, Goldberg NB, Fischer D, *et al.* Conservative surgery and radiation therapy in breast carcinoma: local recurrence and prognostic implications. *Int J Radiat Oncol Biol Phys* 1989, **17**, 727–732.
19. Recht A, Schnitt SJ, Connolly JL, *et al.* Prognosis following local or regional recurrence after conservative surgery and radiotherapy for early stage breast carcinoma. *Int J Radiat Oncol Biol Phys* 1989, **16**, 3–9.
20. Vilcoq JR, Calle R, Stacey P, *et al.* The outcome of treatment by tumorectomy and radiotherapy of patients with operable breast cancer. *Int J Radiat Oncol Biol Phys* 1981, **7**, 1327–1332.
21. Clarke DH, Lê MG, Sarrazin D, *et al.* Analysis of locoregional relapses in patients with early breast cancers treated by excision

and radiotherapy: experience of the Institut Gustave-Roussy. *Int J Radiat Oncol Biol Phys* 1985, **11**, 137–145.
22. Schnitt SJ, Connolly JL, Recht A, Silver B, Harris JR. Breast relapse following primary radiation therapy for early breast cancer. II. Detection, pathologic features, and prognostic significance. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1277–1284.
23. Pierquin B, Marin L. The past and future of conservative treatment of breast cancer. *Am J Clin Oncol* 1986, **9**, 476–480.
24. Recht A, Hayes DF. Local recurrence. In: Harris JR, Hellman S, Silen W, eds. *Breast Diseases*. Philadelphia, Lippincott, 1987, 508–524.
25. Clark RM: Alternatives to mastectomy—The Princess Margaret Hospital experience. In: Harris JR, Hellman S, Silen W, eds. *Conservative Management of Breast Cancer*. Philadelphia, Lippincott, 1983, 35–46.
26. Atkins H, Hayward JL, Klugman DJ, Wayte AB. Treatment of early breast cancer: a report after ten years of a clinical trial. *Br Med J* 1972, **2**, 423–429.
27. Hayward JL. The Guy's trial of treatments of "early" breast cancer. *World J Surg* 1977, **1**, 314–316.
28. Hayward JL. The Guy's Hospital trials on breast conservation. In: Harris JR, Hellman S, Silen W, eds. *Conservative Management of Breast Cancer*. Philadelphia, Lippincott, 1983, 77–90.
29. Hayward J, Caleffi M. The significance of local control in the primary treatment of breast cancer. *Arch Surg* 1987, **122**, 1244–1247.
30. Lionetto R, Pronzato P, Bertelli F, Ardizzoni A, Conte PF, Rosso R. Survival of patients with relapsing breast cancer: analysis of 302 patients. *Oncology* 1986, **43**, 278–282.
31. Beck JR, Pauker SG. The Markov model in medical prognosis. *Med Decision Making* 1983, **3**, 419–458.
32. Williams A. The value of QALYs. *Health Soc Serv J* 1985, **3**, 3–5.
33. Central Bureau of Statistics (CBS). *Life Tables*, 1981–1985. The Netherlands, Mndstat Bevolk (CBS), 1987, 59–60.
34. Sox HC, Blatt MA, Higgins MC, Marton KI. *Medical Decision Making*. Boston, Butterworths, 1988, 161–166.39.
35. De Haes JCJM. Onderzoek naar de gevolgen van het bevolkingsonderzoek naar borstkanker voor de kwaliteit van leven. In: Koning de HJ, Ineveld van BM, Ootmarssen van GJ, *et al. De Kosten en Effecten van Bevolkingsonderzoek naar Borstkanker. Eindrapport.* Erasmus Universiteit, Rotterdam, Instituut Maatschappelijke Gezondheidszorg, 1990, 7.2, 1–19.
36. Weinstein MC, Fineberg HV. *Clinical Decision Analysis*. Philadelphia, Saunders, 1980.
37. Torrance GW, Feeny D. Utilities and quality-adjusted life years. *Int J Tech Assess Health Care* 1989, **5**, 559–575.
38. Pauker SG, Sonnenberg FA, Kassirer JP. Decision Maker, Version 6.1.01, Boston, 1988.
39. Kassirer JP, Pauker SG. The toss-up. *N Engl J Med* 1981, **305**, 1467–69.
40. Bartelink H, Borger JH, Dongen van JA, Peterse JL. The impact of tumor size and histology on local control after breast-conserving therapy. *Radiat Oncol* 1988, **11**, 297–303.
41. Boyages J, Recht A, Connolly JL, *et al.* Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiat Oncol* 1990, **19**, 29–41.
42. Zafrani B, Vielh P, Fourquet A, *et al.* Conservative treatment of early breast cancer: prognostic value of the ductal *in situ* component and other pathological variables on local control and survival. *Eur J Cancer Clin Oncol* 1989, **25**, 1645–1650.

Acknowledgement—This study was supported by grant no. TA 8813 from the Dutch Ministry of Health.

Eur J Cancer, Vol. 27, No. 9, pp. 1137–1140, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Double-blind Randomised Trial of the Antiemetic Efficacy and Safety of Ondansetron and Metoclopramide in Advanced Breast Cancer Patients Treated with Epirubicin and Cyclophosphamide

Norbert W. Marschner, Matthias Adler, Gerd A. Nagel, Dietmar Christmann, Edgar Fenzl and Bahrat Upadhyaya

Ondansetron was compared with metoclopramide for antiemetic efficacy in a randomised double-blind trial in 122 patients with advanced breast cancer. All patients were treated with epirubicin (> 50 mg/m²) and cyclophosphamide (> 500 mg/m²). 50 patients receiving ondansetron and 60 with metoclopramide were considered evaluable. Ondansetron was at least as effective as metoclopramide in the control of vomiting and nausea. The percentage of patients with complete plus major control was 72% (59–85%) vs. 61% (48–74%) on day 1 ($P = 0.230$) and 79% (67–91%) vs. 66% (53–78%) on days 2–3 after chemotherapy ($P = 0.122$). Over the 3-day study period, nausea was absent or mild in 60% of the patients treated with ondansetron, compared to 45% given metoclopramide ($P = 0.064$). No major drug-related side-effects were reported. 1 patient receiving ondansetron experienced gastrointestinal disturbance and headache. Episodes of diarrhoea, fever, hyperkinetic syndrome, fatigue, restlessness and migraine with vomiting were reported by 5 patients treated with metoclopramide. None of the changes in the biochemical or haematological parameters was attributed to the antiemetic treatments.
Eur J Cancer, Vol. 27, No. 9, pp. 1137–1140, 1991.

INTRODUCTION

CYCLOPHOSPHAMIDE-CONTAINING combinations have contributed significantly in the treatment of patients with disseminated breast cancer [1].

Nausea and vomiting, however, are well known side-effects of chemotherapy. Over 80% of patients receiving the combination 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) [2] or cyclophosphamide, methotrexate and 5-fluorouracil