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FIFTH YEAR STUDENT ELECTIVES: REPORT TO THE MYRE SIM BEQUEST COMMITTEE

THE MANAGEMENT OF BREAST CANCER: FACTORS INFLUENCING SURVIVAL FOLLOWING INITIAL DISEASE RECURRENCE

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The use of cytotoxic agents, often in combination, is effective treatment for the majority of patients with metastatic breast cancer. Reports in the early 1980s showed overall response rates of 50-80%, with the duration of survival after chemotherapy averaging 18-24 months.[1] The clinical course of patients with metastatic breast cancer, however, remains highly variable. Many groups have examined factors which may influence response to chemotherapy, or factors affecting prognosis in general. A much smaller number of investigators, for example Clark *et al*,[2] have evaluated factors which may influence survival from the time of first relapse.

Response to first-line chemotherapy is related to the sites of metastasis:[3,4] liver metastases in particular have been associated with a poorer response to chemotherapy. Recurrences in soft tissue, bone, and viscera have been associated with sequentially worse survival.[2] Other factors shown to correlate with the outcome of metastatic breast cancer after treatment include the patient's age,[5,6,7] response to chemotherapy,[5,7,8] tumour's oestrogen receptor (ER) status[2,9] and tumour size.[6,9]

In 1982, the current trend in treatment for systemic therapy of metastatic breast cancer was endocrine therapy with tamoxifen, aminoglutethimide, progestins or androgens, and these agents were useful for 50% of patients either before or after chemotherapy. However, combination chemotherapy was effective in approximately 75% of the patients and offered the best palliation for the majority of the patients.[10] These treatment trends apply to the time-period of the study which I carried out in Edinburgh in 1996/97. A similar report in 1995, by Berkowitz and Love, suggests that earlier systemic therapy can delay and possibly prevent the progression of micro-metastatic disease.[11]

The aim of this study was to evaluate the parameters which may influence a patient's prognosis following the initial recurrence of their disease; such parameters include their initial disease-free interval, age at which chemotherapy was commenced, whether or not they were treated with adriamycin, their response to chemotherapy and the sites of metastases at the time of initial chemotherapy. This particular study was carried out in Boulder, Colorado. An additional aim was to compare the results from this and a previous study carried out in Edinburgh, such that the effect of different treatment protocols on survival could be compared.

I have carried out a retrospective cohort study of patients who received at least one chemotherapy regimen for metastatic breast cancer.

PATIENTS AND METHODS

Data were collected for 95 available sequential patients who received chemotherapy

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for relapse of malignant breast tumours. Selection was made from patients who had attended Boulder Valley Oncology LLP, Boulder, Colorado. All patients had been diagnosed as having primary breast carcinoma between 1971 and 1985, and received chemotherapy for metastatic disease between 1984 and 1996. Forty-seven patients had also received adjuvant chemotherapy some time prior to disease recurrence.

Disease-free interval (DFI) was measured from the date of first recorded diagnosis of primary breast cancer, to first recurrence, which was taken as the first sign of disease relapse following diagnosis. For patients who were still alive at the time of analysis, date of death was taken as the last day of analysis, 15 August 1997. This data was recorded as 'censored'.

POTENTIAL PROGNOSTIC FACTORS

The following information was recorded at the time of data analysis: 1) date of diagnosis; 2) date of initial recurrence; 3) date of first chemotherapy; 4) age at first chemotherapy treatment; 5) disease-free interval (DFI); 6) treatment with or without adriamycin; 7) response to chemotherapy; 8) sites of metastases at first chemotherapy; 9) date of death; 10) time from recurrence to death; 11) time from chemotherapy to death.

Sites of metastases were recorded initially as: lung only; liver only; soft tissue only; bone only; other (non-visceral); visceral and other (any); multiple non-visceral; multiple visceral. These were then further classified into visceral or non-visceral. Various methods of identification were used such as CXR, CT scan and bone scan, depending on the metastases searched for.

All data collected were entered into a computerised database (SPSS for Windows).

CRITERIA FOR RESPONSE

Response to chemotherapy was recorded at the time of note review by an independent observer not associated with any of the patients or recorders and who was only responsible for reviewing the data recorded in the notes. Standard UICC criteria (Table 1) was used for this classification. Data was further classified into complete response and partial response or no response and progressive disease.

TABLE 1
UICC response criteria.

(1)	Complete R	Disappearance of all clinical evidence of active tumour for a minimum of 8 weeks.
	Partial R	50% or more ↓ is the sum of products of the largest perpendicular diameters of measurable lesions, provided no lesions ↑ in size and no new lesions appeared.
(2)	Stable D	No change in tumour dimensions for a minimum of 8 weeks.
	Progressive D	An unequivocable 25% ↑ in size of any measurable lesions or the appearance of new lesions.

STATISTICAL ANALYSIS

The outcome variable was survival, measured from the time of initial recurrence. Curves plotted to show the distribution of survival times for groups of patients were calculated by the method of Kaplan and Meier.[12] Cox's proportional hazards model[13] was used to evaluate the relationship between outcome and individual variables. The comparison of univariate survival distributions of categorical variables was made by Cox's

proportional hazards model. A deviation contrast method was used for 'treatment with/without adriamycin' and 'sites of metastases', for 'response to chemotherapy' a polynomial contrast method was used. The enter method was used to process the variable blocks within a Cox's model. Potential prognostic factors were analysed in multivariate analysis using Cox's proportional hazards model.

Statistical significance was taken as $p \leq 0.05$. All analysis were performed using 'SPSS for Windows' statistical software.

RESULTS

Ninety-five patients who were diagnosed as suffering from primary breast cancer during the 32-year period from 1962 to 1994 were included in this study. Eleven patients were alive at the time of analysis, the median follow-up time of those individuals still alive was 388 weeks, the minimum follow-up time being 195 weeks and the maximum being 1,103 weeks.

The demographic characteristics of the study group of 95 patients are shown in Table 2.

TABLE 2
Demographic characteristics of the study group of 95 patients.
Age at chemotherapy: mean, 58 years; range 28-83.
Disease-free interval(DFI): median, 167 weeks; range 5-1441.

		N	%
Treatment with adriamycin	Yes	77	81.1
	No	18	18.9
Response to chemotherapy-1*	Complete response (CR)	3	3.2
	Partial response (PR)	30	31.6
	No response (NR)	33	34.7
	Progressive disease (PD)	28	29.5
	Not evaluable	1	1
Response to chemotherapy-2*	CR + PR	35	37.2
	NR + PD	59	62.8
Sites of metastases-A†	Lung only	5	5.3
	Liver only	3	3.2
	Soft tissue only	2	2.1
	Bone only	23	24.2
	Other (non-visceral)	3	3.2
	Visceral+other (any)	48	50.5
	Multi-non-visceral	10	10.5
	Multi-visceral	1	1.1
Sites of metastases-B†	Visceral	56	58.9
	Non-visceral	39	41.1

	Median(weeks)	SE	95% c.i.
Survival from initial recurrence of disease‡	107	14	79-135
Survival following first line chemotherapy‡	83	7	70-97

*See Table 1 for response criteria.
†A=separate site, B=accumulated sites.
‡Estimated from Kaplan-Meier survival curves.

The mean age at which patients received first-line chemotherapy was 58 years (range, 28-83 years). The median DFI was 167 weeks, (range, 5-144 weeks). Thirty-seven per

cent of all patients showed some response to first-line chemotherapy, whereas 63% showed no response or progressive disease and 1% were not evaluable.

Survival following initial recurrence of disease is shown in Figure 1.

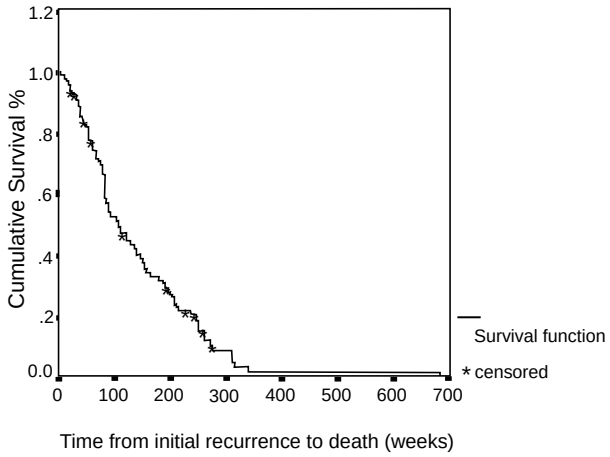

FIGURE 1
Survival after initial recurrence of disease (n=95). The median survival after initial recurrence of disease was 107 weeks (SE,14; 95% c.i.79-135). For patients still alive at the time of analysis, date of death was taken as the last day of analysis (this data was recorded as 'censored').

Table 3 shows additional survival data which includes median survival times and the percentiles of these times for the categorical data analysed.

TABLE 3
Survival data of categorical variables.

		No. patients	Median survival time (weeks)	Percentiles of survival time (weeks) 75	50	25
Adriamycin treatment	Yes	77	107	202	106.71	60.71
	No	18	191	277.14	190.57	76.43
Response to chemo-1*	Complete response	3	313	313.43	313.43	90
	Partial response	30	110	189.57	110.14	81.86
	No response	33	153	249.86	152.57	71.14
	Progressive disease	28	75	119.14	75.29	33.43
Response to chemo-2*	CR + PR	35	110	206.71	110.14	82.14
	NR + PD	59	107	206.71	107	53.14
Sites of metastases-A†	Lung only	5	91	110.14	91	82.14
	Liver only	3	11	40.57	11	3.57
	Soft tissue only	2	54	682.29	54.43	54.43
	Bone only	23	151	206.71	151.14	81.29
	Other (non-visceral)	3	272	271.86	271.86	23.39
	Visceral+other (any)	48	90	202	90.43	60.86
	Multi-non-visceral	10	177	206.71	177.43	90
	Multi-visceral	1	14	14.29	14.29	14.29
Sites of metastases-B†	Visceral	56	83	187.71	83.14	46.43
	Non-visceral	39	151	249.71	151.14	81.29

*See Table 1 for response criteria.
†A=separate site, B=accumulated sites.

The results of univariate analysis are shown in Table 4. Age at chemotherapy, DFI, response and sites of metastases showed a significant association with survival following disease recurrence. Adriamycin treatment was not a significant predictor of survival following disease recurrence in this set of patients. The relationship between response to chemotherapy and survival following initial recurrence is shown in Figure 2.

TABLE 4
Univariate analysis of variables using Cox's proportional hazards model.

Variable	X^2	P	Hazard ratio	95% c.i. for HR lower	upper
Age	5.5225	0.0188	0.9790	0.9618	0.9965
DFI-1	9.2937	0.0023	0.9980	0.9967	0.9993
Treatment with adriamycin	2.0188	0.1554	1.5156	0.8540	2.6898
Response to chemotherapy(overall)-1	10.0356 (r=0.0824)	0.0183	1.3551	1.0391	1.7673
Response to chemo.-2*	0.9951	0.0318	1.2619	0.7990	1.9929
Sites(overall)-1	32.16	0.0000	1.0185	0.8783	1.1810
Sites-2	3.0689	0.0798	1.4909	0.9537	2.3306

*Grouped response to chemotherapy into two categories: a)complete and partial response; b)no response and recurrent disease.

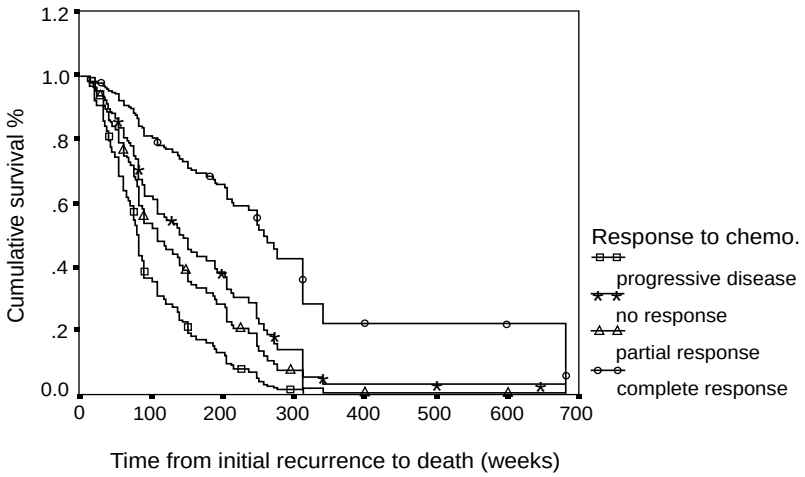

FIGURE 2
Survival after initial recurrence of disease by response to chemotherapy
(n=95, x^2=10.0356, p=0.0183).

Median survival for patients showing complete response was 313 weeks, partial response 110 weeks, no response 153 weeks and progressive disease 75 weeks ($p<0.05$).

The results of univariate analysis for sites of metastases are shown in Table 5. Metastases in liver, soft tissue, bone, viscera and other and multiple non-visceral sites show a significant association with survival following initial disease recurrence. Metastases in the lung and other (non-visceral) sites did not show a significant association with survival. Further classification into metastases at visceral or non-visceral sites showed a close to significant association with survival. The relationship between sites of metastases and survival can be seen in Figure 3. The median survival for those with

TABLE 5
Univariate survival analysis for sites of metastases.
(With reference category taken as multi-visceral metastases.)

Variable	X^2	df	p	HR	95% c.i. for HR lower	upper
Sites-A*	32.1574	7	0.0000			
Lung	1.6796	1	0.1950	0.519	0.1930	1.3985
Liver	16.5859	1	0.0000	11.3660	3.5285	36.6125
Soft tissue	5.4129	1	0.0200	0.1163	0.0190	0.7125
Bone	6.0582	1	0.0138	0.4476	0.2360	0.8490
Other(non-visc.)	1.6156	1	0.2037	0.4268	0.1148	1.5864
Visc.+other	4.0683	1	0.0437	0.5625	0.3216	0.9839
Multi non-visceral	5.1299	1	0.0235	0.4025	0.1831	0.8847
Sites-B*	3.0698	1	0.0798	1.4909	0.9537	2.3306

*A=separate site, B=accumulated sites.

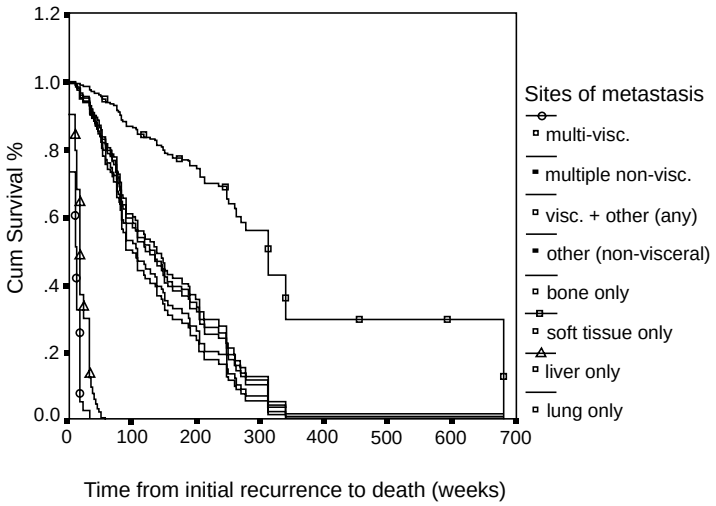

FIGURE 3
Survival after initial recurrence of disease by sites of metastases (n=95, x^2=32.16, p=0.000).

soft tissue metastases is 54 weeks, range 54-682, whereas for metastases in the liver only or, at multi-visceral sites, the median survival time is 11 weeks, range 3-40, and 14 weeks respectively.

The results of multivariate analysis are shown in Tables 6, 7 and 8. Table 6 shows overall results of multivariate survival analysis.

TABLE 6
Overall results of multivariate survival analysis.

X^2	df	p
96.921	13	0.0000

Table 7 shows multivariate survival analysis. DFI shows a significant association with survival, as does complete response and no response to chemotherapy and the

presence of metastases in liver, soft tissue, bone, visceral and other, and multiple non-visceral sites ($p<0.05$).

TABLE 7
Multivariate survival analysis.

Variable	X^2	p	Hazard ratio(HR)	95% c.i. of HR lower	upper
Age at chemo.	2.2349	0.1349	0.9820	0.9590	1.0057
DFI	6.1071	0.0135	0.9981	0.9966	0.9966
Adriamycin treatment	0.0450	0.8320	0.9622	0.6739	1.3739
Response-1* *(with reference to progressive disease)*					
Complete response	7.0205	0.0081	4.3498	1.4622	12.9048
Partial response	1.6822	0.1946	0.5688	0.2425	1.3343
No response	10.6113	0.0011	2.5200	1.4451	4.3945
Response-2*	1.2260	0.2682	1.2014	0.8682	1.6623
Sites *(with reference to multi-visc.)*					
Lung only	0.2047	0.6510	0.7799	0.2657	2.2895
Liver	9.0202	0.0019	9.4885	2.2893	39.3279
Soft tissue	7.8177	0.0052	0.0605	0.0085	0.4323
Bone	6.7081	0.0096	0.3900	0.1912	0.7955
Other (non-visceral)	0.0032	0.9522	0.9589	0.2215	4.1512
Visc.+other	5.1043	0.0239	0.4962	0.2701	0.9113
Multi non-visceral	6.7792	0.0092	0.3211	0.1366	0.7552
Sites-B†	1.6085	0.2047	0.8636	0.6886	1.0832

*See Table 1 for response criteria.
†A=separate site, B=accumulated sites.

The demographic and survival data for both the American and Edinburgh study groups are shown in Table 8.

DISCUSSION

It must be highlighted that the patients included in this study do not represent a random cross-section of patients with primary breast cancer. They all presented with primary disease which subsequently recurred and required chemotherapy treatment.

Similar to results found in other studies,[1,2,3] DFI was found to be an important factor in influencing survival following initial recurrence. The median DFI of the American study was 167 weeks compared to a median DFI of 81 weeks for patients in the Edinburgh study. A possible explanation for this difference may be found by comparing the criteria each group use in deciding whether adjuvant chemotherapy is necessary and how aggressive a treatment is then initiated in the individual patient. Adjuvant chemotherapy has been found in previous studies to be associated with a significantly shorter time to treatment failure;[4] in contrast it has also been found to be associated with a lower local recurrence rate and disease relapse rate.[14,15] If the American protocol is to initiate adjuvant chemotherapy earlier and more aggressively than in the United Kingdom then the results found would support the latter studies which associate adjuvant chemotherapy with a better prognosis. This study did not look at adjuvant chemotherapy in detail. However, it remains a factor whose affect on prognosis is controversial, and further studies are required to ascertain the most ideal protocol for adjuvant chemotherapy treatment.

For some time now age at chemotherapy has been shown to influence survival and

this study is, perhaps, further confirmation of this. Haffty *et al*[14] found young age to be the most significant prognostic factor for local recurrence ($p<0.03$), similar results were also recorded by numerous other groups.[5,6,7]

TABLE 8
Demographic characteristics of the study groups in America and Edinburgh.

	American study group	Edinburgh study group
Age at chemotherapy	mean, 58 years; range 28-83	mean, 55 years; range 31-80
Disease-free interval	median, 167 weeks; range 5-1441	median, 81 weeks; range 0-723

		America		United Kingdom	
		N	%	N	%
Adriamycin treatment	Yes	77	81.1	114	52.3
	No	18	18.9	104	47.7
Response to chemotherapy-1*	Complete response	3	3.2	23	10.6
	Partial response	30	31.6	77	35.5
	No response	33	34.7	33	15.1
	Progressive disease	28	29.5	65	29.8
Response to chemotherapy-2*	CR + PR	35	37.2	110	58.2
	NR + PD	59	62.8	98	41.8
Sites of metastases-A†	Lung only	5	5.3	9	4.1
	Liver only	3	3.2	8	3.7
	Soft tissue only	2	2.1	77	35.5
	Bone only	23	24.2	9	4.1
	Other(non-visceral)	3	3.2	4	1.8
	Visceral + other(any)	48	50.5	66	30.4
	Multi non-visceral	10	10.5	29	13.4
	Multi visceral	1	1.1	15	6.9
Site of metastases-B†	Visceral	56	58.9	98	45.2
	Non-visceral	39	41.1	119	54.8

	Median(weeks)	SE	95% c.i.
<u>American study group</u>			
Survival from initial recurrence of disease‡	107	14	79-135
Survival following first-line chemotherapy‡	83	7	70-97
Time from recurrence to chemotherapy	22		
<u>Edinburgh study group</u>			
Survival from initial recurrence of disease‡	84.29	7.57	69.45-99.13
Survival following first-line chemotherapy‡	52.86	3.48	46.03-59.69
Time from recurrence to chemotherapy	31		

*See Table 1 for response criteria.
†A=separate site, B=accumulated sites.
‡Estimated from Kaplan-Meier survival curves.

As with the previous Edinburgh study, one of the most prominent variables influencing survival following initial disease recurrence was the patient's response to first-line chemotherapy; similar results having been reported by other investigators.[5,7,8] Although complete response and progressive disease were associated with sequentially

worse survival, no response was shown to be a better prognostic factor than partial response. This unexpected result may be explained by the fact that on an individual basis a distinction between the two categories is often quite difficult.

There remains no definitive answer as to what role that sites of metastases, or the number of sites with metastases, play in the prognosis of metastatic breast cancer. Gregory *et al* identified liver metastases as important prognostic factors,[1] similarly Falkson *et al*[3] found liver metastases to be associated with a significantly shorter time-to-treatment-failure and a significantly shorter survival. On univariate survival analysis, soft tissue metastases were shown to be associated with a significantly longer time from initial recurrence to death compared with liver metastases which were associated with a significantly poorer prognosis, see Figure 3. Metastases in multiple non-visceral sites, bone and visceral together with other sites were shown to be significantly associated with a sequentially worse prognosis. In contrast, Hortobagyi *et al*[2] found sites of metastases to be of no prognostic value. Hence the controversy continues as to the importance of sites of metastases in affecting prognosis.

Whether or not the number of sites with metastases affects prognosis is another much discussed issue as some investigators reported that three or more organ sites are associated with a lower probability of response to treatment and a significantly shorter survival,[3] whereas others state that an increased number of sites of disease has no prognostic importance.[1] I would conclude from this study that specific sites appear to be of more prognostic importance than the overall number of sites involved.

On comparing this study carried out in Boulder, Colorado with a similar study of patients at the Western General Hospital (WGH), Edinburgh, it can be concluded that in terms of both disease-free interval and time from initial recurrence to death, those treated in America showed a longer median survival time. These two groups of patients were comparable in terms of age at which chemotherapy was given. Time taken from recurrence to starting chemotherapy was found to be nine weeks shorter in the American study group. Possible factors which could be responsible for this difference, include the readiness at which adjuvant chemotherapy is given in Colorado, the time from initial recurrence of disease to when further chemotherapy was initiated, the types of chemotherapy used, other forms of therapy used and the length of time for which they were used before a decision was made as to whether the response was adequate or not.

The incidence of breast cancer continues to increase and will reach close to one million new patients annually by the year 2000. Effective control requires prevention, early diagnosis, and access to effective treatments.[10] It is therefore essential that the most effective treatment strategies are sought. This preliminary finding indicates that it may be worthwhile analysing further the differences in practice and effectiveness between the UK and USA.

Finally, when planning treatment strategies additional factors which should not be overlooked include the cost-effectiveness of treatment as today the total direct medical costs of breast cancer is more than $7 billion per year worldwide.[10] It is also important when considering the effectiveness of more aggressive therapy regimens to weigh the potential benefits of systemic chemotherapy against the likely toxicities of the agents used as drug toxicities and side-effects remain a prominent feature of chemotherapy.

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