Table 1. Patterns of surgery and TNM distribution by age (total no. of patients 291)

Age group (years)	Surgery			T			N			M		
	CS	PS+ES	NS	1–2	3–4*	X	0	1–2	X	0	1	X
A. <60	37	13	3	38	10	5	18	27	8	38	14	1
	(70)	(25)	(06)	(72)	(19)	(09)	(34)	(51)	(15)	(72)	(26)	(02)
B. 60–69	48	12	12	43	16	13	23	32	17	45	24	3
	(67)	(17)	(17)	(60)	(22)	(18)	(32)	(44)	(24)	(63)	(33)	(04)
C. 70–79†	56	18	26	47	23	30	27	38	35	54	33	13
	(56)	(18)	(26)	(47)	(23)	(30)	(27)	(38)	(35)	(54)	(33)	(13)
D. >79†	17	6	43	17	4	45	10	9	47	18	17	31
	(26)	(09)	(65)	(26)	(06)	(68)	(15)	(14)	(71)	(27)	(26)	(47)
χ^2 for trend	25.6	4.0	52.0	27.7	2.9	49.9	6.0	18.4	42.5	24.5	0.0	46.6
P value	0.0000	0.0454	0.0000	0.0000	0.09	0.0000	0.0146	0.0000	0.0000	0.0000	0.89	0.0000

CS, curative surgery; PS, palliative surgery; ES, explorative surgery; NS, no surgery. Values in parentheses are row percentages (total = 100% for each age group in each column). * The T_3 and T_4 categories include those lesions showing, either on surgical exploration or at laparoscopy, penetration through the serosa and, respectively, involvement of adjacent structures. †Data unavailable for 1 patient.

the amount of clinical data formally evaluable by hospital staff for decisions on treatment decreased with increasing age.

Age-specific proportions of patients undergoing curative surgery in the present series were similar to those observed among GC cases of the SEER cancer registries [7]. A downward trend was evident in both studies. In view of the reduced tolerance to functional changes following major surgery [8], it has been emphasised that a key issue in geriatric surgical oncology is the increased importance of palliation compared to cure [1, 8]. In our series, the most pronounced effect of age was an increase in the frequency of patients not undergoing any type of surgery, with a reduction in the frequency of palliative/explorative approaches, even among patients not having curative surgery. Thus, the relative importance of surgical palliation decreased with increasing age.

GC has never been taken into consideration in studies aimed at evaluating age differences in stage distribution of patients with common types of tumours [9, 10]. Our data are apparently inconclusive because TNM classification of GC patients mirrors the key role of the surgical approach in the staging process. In fact, patient's age appeared to exert an atypical, two-fold effect on stage of GC as compared with other major malignancies, with an age-dependent decrease in the frequency of "early" stage categories being associated with a reverse trend for cases TNM-unclassified.

Our data suggest that age can be a strong determinant of major patterns of GC care.

1. Monfardini S, Aapro M, Ferrucci L, Zagonel V, Scalliet P, Fentiman I. Commission of the European Communities "Europe Against Cancer" Programme, European School of Oncology advisory report. Cancer treatment in the elderly. *Eur J Cancer* 1993, **29A**, 2325–2330.
2. Jensen OM, Estève J, Moller H, Renard H. Cancer in the European Community and its member states. *Eur J Cancer* 1990, **26**, 1167–1256.
3. Parkin DM, Muir CS, Whelan SL, Gao Y-T, Ferlay J, Powell J. Cancer incidence in five continents, Volume VI. IARC Scientific Publications no. 120. Lyon, International Agency for Research on Cancer, 1992.
4. Amadori D. Registro Tumori della Romagna (R.T.Ro.). *Incidenza per Tumori Maligni in Romagna* 1986–1988. Forli, Istituto Oncologico Romagnolo, 1992.
5. International Union Against Cancer. *TNM Classification of Malignant Tumours*, fourth edition. Berlin, Springer Verlag, 1992.
6. Mantel N. Chi square with one degree of freedom. Extension of the Mantel–Haenszel procedure. *J Am Stat Assoc* 1963, **58**, 690–700.
7. Curtis RE, Kennedy BJ, Myers MH, Hankey BF. Evaluation of stomach cancer staging using the SEER population. *Semin Oncol* 1985, **12**, 21–31.
8. Patterson WB. Surgical issues in geriatric oncology. *Semin Oncol* 1989, **16**, 57–65.
9. Goodwin JS, Hunt WC, Samet JM. Determinants of cancer therapy in elderly patients. *Cancer* 1993, **72**, 594–601.
10. Kant AK, Glover C, Horm J, Schatzkin A, Harris TB. Does cancer survival differ for older patients? *Cancer* 1992, **70**, 2734–2740.

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Different Doses of Epirubicin Associated with Fixed Doses of Cyclophosphamide and 5-Fluorouracil: a Randomised Study in Advanced Breast Cancer

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INCREASING ANTHRACYCLINE dosage could ameliorate the antitumour effect in advanced breast cancer (BC). In fact, anthracy-

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clines are the most effective agents in this disease and their steep experimental dose–response curve indicates that even small increases in dosage may ameliorate their cytocidal effect.

Between April 1991 and 1994, 67 consecutive, evaluable patients (≤75 years, performance status ≤2, normal blood counts, blood chemistry and cardiac function) with measurable recurrent or metastatic BC (Table 1) were randomly treated with different dosages of epirubicin (75 versus 100 mg/m^2, day 1) associated with the same dosage (600 mg/m^2 day 1) of cyclophosphamide and 5-fluorouracil (75 versus 100-FEC (5-fluorouracil–epirubicin–cyclophosphamide)). Patients were scheduled to receive six courses at 21 day-intervals. With granulocytes <500 μl on day 14, patients received subcutaneously granulocyte colony stimulating factor (G-CSF, 5 μg/kg/day). With platelets <75 000/μl on day 21, chemotherapy had to be delayed or reduced. Toxic effects and tumour response (at fourth course) were assessed according to WHO criteria (the UICC criteria for response were used in patients with only assessable bone metastases). Dose intensity (DI) was calculated for epirubicin at the fourth course.

A total of 375 courses (198 in 75- and 177 in 100-FEC) (89% of planned) were administered on an outpatient basis. The mean number of courses was 4.7 and 4.9 in 75- and 100-FEC regimens, respectively. The actual delivered DI for epirubicin was 25.2 and 30.2 mg/m^2/week in 75- and in 100-FEC, respectively, which indicates an increase in the epirubicin dosage of approximately 18% in 100-FEC with respect to 75-FEC.

Table 1. Main clinical characteristics and outcome of treatment in evaluable patients who were randomised for treatment with 75-FEC or 10-FEC regimens

	FEC-75	FEC-100	Total
No. of evaluable patients	35	32	67
Age (median, years)	60	55	67
Performance status			
0	25	24	49
1	8	7	15
2	2	1	3
Previous CMF ± TAM	4	3	7
Previous RFI (mos)	39 (0–308)	33 (0–136)	37 (0–308)
Sites of disease			
Viscera ± other	23	22	45
Soft tissues	4	6	10
Loco-regional only	2	1	3
Bone only	6	3	9
Objective response (no. (%))			
CR + PR	18 (51)	18 (56)	36 (54)
CR	8 (23)	12 (38)	20 (30)
PR	10 (28)	6 (19)	16 (24)
NC	8 (23)	6 (19)	14 (21)
PD	9 (26)	8 (25)	17 (25)
Time to progression, median (mos)	10	11	10.5
Survival, median (mos)	13	22	16

FEC, 5-fluorouracil (600 mg/m^2) + epirubicin + cyclophosphamide (600 mg/m^2); 75-FEC, FEC with epirubicin 75 mg/m^2; 100-FEC, FEC with epirubicin 100 mg/m^2; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; TAM, tamoxifen; RFI, relapse-free interval; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; mos, months.

Both non-haematological and haematological toxicities were similar in 75-FEC and 100-FEC, and did not cause delays or dose reductions. The most common side effects were grade II nausea and vomiting and grade III alopecia. Granulocytopenia was slightly more pronounced in the 100- than in 75-FEC arm (G-CSF was needed in 15% of 100-FEC and 4% of 75-FEC courses).

Overall response and disease progression rate, as well as time to progression, were similar in the 75-FEC and 100-FEC regimens (Table 1). Complete responses were slightly more frequent (38 versus 23%, ns) and survival more prolonged (22 versus 13 months, $P < 0.09$) in patients treated with 100-FEC compared to those treated with the 75-FEC regimen.

From these data, a moderate (18%) increase in the dosage of epirubicin, included into the FEC regimen, is feasible in patients with advanced breast cancer and possibly improves the antitumour effect.

These results concur with those from recent literature, where increasing anthracycline dosage with [10–18] or without [1–9] CSF support, was consistently linked with some improvement of one or more commonly measurable indexes of antitumour effects, namely response rate and/or duration of response and/or survival, with no study reporting a worsening of these indexes.

Response rate is usually improved. In randomised studies, a greater median rate of total (58 versus 41%) and especially of complete responses (21 versus 7%) has been obtained, with higher rather than lower doses of anthracyclines, administered alone [2–5, 7] or associated with fixed doses of cyclophosphamide and 5-fluorouracil (FEC regimens) [1, 7–9]. Several non-randomised [10–17] and randomised [18] studies have further increased the anthracycline (± other drugs) dosage with programmed CSF support, which resulted in response rates of 64–100% (median 81%).

Advantages in response and survival duration are less evident. In randomised studies, median response durations were 14 (9.2–22) and 9.5 (5.4–14) months [2, 4, 6, 7, 18] with the higher and lower anthracycline dosages, respectively. Survival durations were 18 (11–21) and 12 (9–21) months, respectively [1–4, 6, 7, 18]. In non-randomised studies with high dose anthracycline and CSF support, survival durations were 16–30 months [10–18].

These data point to at least some improvement in antitumour effect with increasing drug dosage, but the overall clinical validity of this policy in a palliative setting needs to be integrated with the appropriate evaluation of quality of life, which is remarkably lacking in most reported studies. In an ongoing randomised study, we are now evaluating how quality of life is affected by the increased drug- or CSF-related side effects, and the psychological distress linked to expectancy of this toxicity.

1. Hortobagyi GN, Bodey GB, Buzdar AU, *et al.* Evaluation of high-dose versus standard FAC chemotherapy for advanced breast cancer in protected environment units: a prospective randomized study. *J Clin Oncol* 1987, 5, 354–364.
2. Carmo-Pereira J, Oliveira-Costa P, Henriques E, *et al.* A comparison of two doses of the adriamycin in the primary chemotherapy of disseminated breast cancer. *Br J Cancer* 1987, 56, 417–473.
3. Habeshaw T, Paul J, Jones R, *et al.* Epirubicin at two dose levels with prednisolone as treatment for advanced breast cancer: the results of a randomized trial. *J Clin Oncol* 1991, 9, 295–304.

4. French Epirubicin Study Group. A prospective randomized trial comparing epirubicin monochemotherapy to two fluorouracil, cyclophosphamide and epirubicin regimens differing in epirubicin dose in advanced breast cancer patients. *J Clin Oncol* 1991, **9**, 305–312.
5. O'Brian RM, Baker LH, Gottlieb JE, *et al.* Dose response evaluation of adriamycin in human neoplasia. *Cancer* 1977, **39**, 1940–1948.
6. Focan C, Andrien JM, Closon MT, *et al.* Dose–response relationship of epirubicin-based first-line chemotherapy for advanced breast cancer: a prospective randomized trial. *J Clin Oncol* 1993, **11**, 1253–1263.
7. Blomquist C, Elomaa I, Rissanen P, Hietanen P, Nevasaari K, Helle L. Influence of treatment schedule on toxicity and efficacy of cyclophosphamide, epirubicin and fluorouracil in metastatic breast cancer: a randomized trial comparing weekly and every-4-week administration. *J Clin Oncol* 1993, **11**, 467–473.
8. Marschner N, Kreienberg R, Souchon R, *et al.* Evaluation of the importance and relevance of dose intensity using epirubicin and cyclophosphamide in metastatic breast cancer: interim analysis of a prospective randomized trial. *Semin Oncol* 1994, **21**, 10–16.
9. Colajori E, Tosello C, Pannuti F, *et al.* Randomized multinational trial comparing epirubicin (EPI) 50 mg/mq vs 100 mg/mq in combination with 5-fluorouracil (5FU) and cyclophosphamide (CTX) as front line treatment of metastatic breast cancer (MBC). Abstr. ESMO Congress, Lisboa, 21 November 1994. *Ann Oncol* 1994, 5 (suppl. 8), 26, abstr. 126.
10. Fountzilas G, Skarlos D, Giannakakis T, *et al.* Intensive chemotherapy with high dose epirubicin every 2 weeks and prophylactic administration of filgrastim in advanced breast cancer. *Eur J Cancer* 1994, **30**, 965–969.
11. Bronchud MH, Howell A, Crowther D, Hopwood P, Souza L, Dexter TM. The use of G-CSF to increase the intensity of treatment with doxorubicin in patients with advanced breast cancer. *Br J Cancer* 1989, **60**, 121–125.
12. O'Shaughnessy JA, Denicoff AM, Venzon DJ, *et al.* A dose intensity study of FLAC (5 fluorouracil, leucovorin, doxorubicin, cyclophosphamide) chemotherapy and *Escherichia Coli* derived granulocyte-monocyte-colony stimulating factor (GM-CSF) in advanced breast cancer patients. *Ann Oncol* 1994, 5, 709–716.
13. Ferguson JE, Dodwell DJ, Seymour AM, Richards MA, Howell A. High dose, dose-intensive chemotherapy with doxorubicin for the treatment of advanced breast cancer. *Br J Cancer* 1993, **67**, 825–829.
14. Van Hoef HM, Baumann I, Lange C, *et al.* Dose-escalating induction chemotherapy supported by lenograstim preceding high-dose consolidation chemotherapy for advanced breast cancer. Selection of the most acceptable regimen to induce maximal tumour response and investigation of the optimal time to collect peripheral blood progenitor cells for haematological rescue after high-dose consolidation chemotherapy. *Ann Oncol* 1994, 5, 217–224.
15. Osborne CK, Sunderland MC, Neidhart JA, Ravdin PM, Abeloff MD. Failure of GM-CSF to permit dose-escalation in an every other week dose-intensive regimen for advanced breast cancer. *Ann Oncol* 1994, 5, 43–47.
16. Ogawa M. High dose epirubicin studies on metastatic breast cancer in Japan. In Abstr Satellite Symposium ESMO Congress: Intensive therapy for solid tumours: epirubicin. Lisboa, 21 November 1994, p. 16.
17. Scinto AF, Cercato MC, Botti C, *et al.* Phase II trial of high dose epirubicin and cyclophosphamide in advanced breast cancer. *Eur J Cancer* 1994, **30A**, 1285–1288.
18. Ardizzoni A, Venturini M, Sertoli MR, *et al.* Granulocyte-macrophage colony-stimulating factor (GM-CSF) allows acceleration and dose intensity increase of CEF chemotherapy: a randomized study in patients with advanced breast cancer. *Br J Cancer* 1994, **69**, 385–391.

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Non-cytotoxic CD4 Tumour-infiltrating Lymphocytes Induce Responses in Patients with Metastatic Renal Cell Carcinoma Previously Treated with Interleukin-2

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WE PREVIOUSLY reported the lack of therapeutic effect of tumour-infiltrating lymphoytes (TIL) in patients with metastatic melanoma who have failed to respond to high-dose interleukin 2 (IL2) [1]. In order to test the ability of TIL to modify IL2 response in renal cell carcinoma (RCC), we treated, in a preliminary study, 6 patients. 4 patients had previously received high-dose IL2 and 2 had received a subcutaneous low dose. The characteristics of patients are summarised in Table 1, all were metastatic predominantly in lymph nodes and lung. Two types of response were observed: in 2 patients, who were partial responders to IL2 alone (patients 2 and 3), infusion of their TIL induced complete responses; in 2 other patients, whose tumour progressed after IL2 alone (patients 4 and 6), the infusion of TIL resulted in a stabilisation of the disease. These observations are in agreement with the theory proposed by Greenberg [2] of TIL efficacy when tumour burden is reduced. The second observation may also indicate that TIL may be efficacious without an IL2 effect, although this was only partial efficacy. The phenotype of these 4 patients was predominantly CD4, but with 30–40% of CD8-positive cells in 2 patients. More interestingly, the TIL exerted little or no cytotoxicity towards various targets, including autologous tumour (Table 1), whereas autologous cytotoxicity has been reported to be associated with response in melanoma [3]. This leads us to propose that other mechanisms, such as cytokine production by CD4+ T helper cells, are effective in RCC tumour control [4].

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