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Letters

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Comments on: *Survival of Colorectal Cancer Patients in Europe during the Period* 1978–1989, Gatta, et al., *Eur J Cancer* 1998, 34, 2176–2183

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I AM writing regarding the publication of Gatta and colleagues [1]. This is obviously a very important study, as is the whole of the EUROCARE study, and those results should be analysed very carefully by all European oncologists as well as each country's health authorities. I have only one reservation about what I think represents a potential statistical bias.

It appears from the 5-year relative survival figures by country, shown in Figure 3, that all countries, apart from Finland, that have poorer registry records (6–20% of the total population) also appear to have better survival. In contrast, of the countries with better registries (20–100% of the total population), all but Polish and Austrian women have poorer survival. This gives the impression that the presence of a better or complete registry may be associated with poorer survival. This is difficult to understand. Although the sizes of the samples in all countries are adequate for statistical comparison there is a possibility of bias.

One could claim that in countries with poorer registries, university hospitals and specialised cancer units might be over-represented with a higher proportion of patients. Alternatively, smaller district or remote hospitals might not report enough cases.

In contrast, in countries with registration of 80–100% of colorectal cancer cases, a greater variability of treatment or lack of treatment by specialists might give a worse picture.

What Gatta and colleagues should do is to break down each country's cases according to management in teaching hospitals/specialised units as opposed to district hospitals. This might not be an easy task and it would certainly complicate the subgroup analysis. However, it would be the only way to prove their point beyond any doubt. For the time being, for those who have a deeper knowledge of research methods, this doubt remains.

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1. Gatta G, Faivre J, Capocaccia R, Ponz de Leon M and the EUROCARE Working Group. Survival of colorectal cancer patients in Europe during the period 1978–1989. *Eur J Cancer* 1998, **34**, 2176–2183.

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Response from G. Gatta, J. Faivre, R. Capocaccia, *et al.*

G. Gatta, J. Faivre, R. Capocaccia, M. Ponz de Leon and the EUROCARE Working Group

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I AGREE WITH Dr Papagrigoriadis's statement regarding the comparability problem arising from the variable national coverage of cancer registration, ranging from 100% in northern and some eastern European countries to less than 10% in countries of southern and central Europe. In the latter, the areas covered by registries may not be representative of the whole nation. Small registries in particular may be more likely to be present in areas where the local medical community has an above average interest in oncology, and this could positively influence the standard and availability of care in those areas [1]. However, Spain, France, Switzerland and The Netherlands have, in fact, a much larger coverage than suggested by their participation in EUROCARE II. I do not think that the registries from these countries that participated in EUROCARE II did so because of the possible bias mentioned by Dr Papagrigoriadis. It is worth noting also that the number of cancer registries increased in EUROCARE II compared to EUROCARE I and several countries were much better represented. This was the case with France, The Netherlands, Spain, Italy, Poland and England, and the rank of cancer survival for these countries did not change between the studies.

Dr Papagrigoriadis suggested analysing survival by type of hospital (specialised versus district hospitals) as one would expect better survival for the former. I disagree with this because of stage migration [2]. With modern staging techniques a fraction of cancers previously classified as localised are recognised as at a more advanced stage, apparently improving the prognosis for both stages. The new diagnostic techniques are not available at the same time in different countries or in different hospitals within a given country or

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region, affecting not only stage-specific survival comparisons between populations, but also between different types of hospital. Similarly, clinicians in specialist oncological institutions are more likely to carry out more exhaustive and 'aggressive' staging to establish appropriate therapy, and enrol their patients in clinical trials.

Knowledge, not only of disease stage at diagnosis but also the staging procedures used to define that stage is, therefore, vital for interpreting survival differences. Unfortunately, information on the diagnostic procedures used for defining disease stage is rarely available to population-based cancer registries. The EUROCARE Working Group is seeking to obtain information on disease stage, staging procedures and treatments for a representative sample of incident cases in European populations for colorectal, breast, testis, stomach and prostate cancers (data not shown). A major EUROCARE priority is to carry out stage-specific survival comparisons, based on the staging procedures actually used. Controlling for these variables will enable us to assess the extent to which survival differences depend on different treatments or differences in treatment effectiveness in relation to early versus late diagnosis.

1. Berrino F, Gatta G, Chessa E, Valente F, Capocaccia R. and the EUROCARE Working Group. Introduction: the EUROCARE II study. *Eur J Cancer* 1998, **34**, 2139–2153.
2. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985, **312**, 1604–1608.

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Comments on: *Treatment of Metastatic Malignant Melanoma with Dacarbazine Plus Fotemustine*, Seeber, *et al.*, *Eur J Cancer* 1998, 34, 2129–2131

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We read with interest the paper of Seeber and colleagues [1] that reported on the clinical activity of a regimen including dacarbazine (DTIC) 200 mg/m^2 on day 1 and fotemustine (FM) 100 mg/m^2 on day 2, recycled every 4 weeks in 63 patients (14 of whom were previously treated with chemotherapy) with advanced melanoma. These authors observed 3 complete and 4 partial responses, for an overall response rate of 11% (95% confidence interval (CI) 5–22%). Although no overall survival of the whole series was reported, it can be argued from their Figure 1, showing survival curves according to response to treatment that the median duration of survival of this population should have been approximately 6–7 months, corresponding to the median survival time of the patients (52%) showing stable disease with this regimen. We also have utilised a combination of DTIC + FM, with the addition of r-interferon α between courses, for the treatment of patients with advanced melanoma [2]. However, we have administered FM 100 mg/m^2 on day 1, followed by DTIC 250 mg/m^2 on days 2–5, every 3 weeks, obtaining 4 complete and 13 partial responses among 43 chemonaïve (but 22 had previously received adjuvant interferon α) patients with advanced melanoma, for an overall response rate of 40% (95% CI 25–56%). The median survival time of our series was 40 weeks and the 2 year probability of survival was 13%. We have subsequently conducted a further trial testing the addition of cisplatin (CDDP), 25 mg/m^2 on days 3 and 4 to a regimen including FM 100 mg/m^2 on day 1 and DTIC 300 mg/m^2 on days 2–4, recycling every 3–4 weeks, with granulocyte macrophage-colony stimulating factor (GM-CSF) support when needed. Among 60 chemonaïve patients, 11 complete and 12 partial responses were registered, for an overall activity rate of 38% (95% CI 26–62%). The median survival time resulted of 39 weeks and the 2 year projected survival was 32% [3]. Therefore, based on our whole experience of more than 100 treated patients, we are confident that at least 30% of patients treated with a regimen including FM + DTIC ± CDDP could reach a major response and that some of them may also enjoy prolonged survival. Although the comparison of results obtained in different series of patients is always difficult to interpret and therefore should be considered with caution, we wonder why Seeber and colleagues reported such dismal activity with their regimen. A possible explanation might be the dosages and schedule they adopted, with an unusual low dose of DTIC given every 4 weeks, that translated into a poorly intensive treatment. Their aim was to avoid the life-threatening pulmonary toxicity from DTIC + FM combination. However, this kind of unpredictable toxicity has been reported only when both drugs were administered together on the same day [4–6]. On the contrary, when DTIC was given at increasing doses (400, 500, 800 mg/m^2) 4 h before FM (100 mg/m^2) every 4 weeks, the resulting response rate was linearly related to DTIC dosage, being 24, 30 and 40%, respectively [6], confirming the clinical relevance of an adequate treatment. In our experience with the FM + DTIC sequential treatment, no patient suffered from pulmonary side-effects and no difference in activity according to main metastatic site was observed in either series. Therefore, when the drugs are given 24 h apart, a peculiar cytotoxicity on lung tissues could be ruled out. Since we share the hope of Seeber and coworkers that an objective remission may be associated with longer survival, we also believe that, in the palliative treatment of the advanced disease, every effort should be made to deliver active combination chemotherapy at the maximum recommended dose to increase the likelihood of achieving a rapid tumour shrinkage without excessive toxicity.

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