of this potential side-effect. The treatment of early breast cancer with cytotoxic chemotherapy is aimed as a cure of a potentially fatal disease, and onycholysis of toe nails may well be acceptable to patients in view of the benefit. However, the treatment of metastatic breast cancer aims at palliation and in this situation careful consideration needs to be given to avoiding any side-effects that could potentially impair quality of life.

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Prevention of Second Primary Tumours With a Second Generation Retinoid in Squamous Cell Carcinoma of Oral Cavity and Oropharynx: Long Term Follow-up

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IT HAS been suggested that retinoids might be used as a pharmacological approach to the chemoprevention of cancer, because of their ability to exert a hormone-like control over normal cellular differentiation and proliferation, which may subsequently influence neoplastic development [1, 2]. Hong and associates and Benner and associates [3, 4] have shown that treatment with isotretinoin following primary therapy for squamous cell cancer of the head and neck reduces significantly the development of second primary tumours. In 1985, we launched a double-blind randomised study of T1/T2, N0/N1 < 3 cm, M0, clinical stage carcinoma of oral cavity and oropharynx trial by choosing etretinate, a second generation retinoid [5]; at that time, we had no data concerning the effect of etretinate on head and neck cancer or oral leukoplakia. 316 patients with histologically confirmed primary squamous cell carcinoma were randomly assigned to receive 2 years of therapy with either etretinate (156 patients) at a dose of 25 mg per day or placebo (160 patients). Eighty-two per cent of the tumours were located in the oral cavity. Five per cent of the patients in the etretinate group (8/156) and three per cent in the placebo group (5/160), were entered in the study but were not controlled after completion of primary treatment. In addition, 51 patients in the etretinate group (33%) and 36 in the placebo group (23%) did not complete the 24-month course of treatment because of clinical or biological toxicity, a relapse or other reasons; severe side-effects were described in detail in the initial report [6], based on a median follow-up of 41 months: the 5-year projected rates of development of second primary tumours were 38% in the etretinate group and 24% in the placebo group (NS).

We report here the long-term results based on 316 patients with a mean follow-up of 65 months. We found no difference in the survival curves of the two groups (log-rank NS): the 5-year survival rate (95% confidence interval) in the etretinate group is 65% (56–72) versus 74% (66%–81%) in the placebo group. There are no differences regarding local or regional relapses (log-rank NS) and distant metastasis (log-rank NS). 42 patients in the etretinate group and 40 in the placebo group developed a second primary tumour. In more than 75% of the cases, the second primary tumour occurred in the head and neck, oesophagus or lung, which is in keeping with the concept that the occurrence of neoplastic disease in these areas is tobacco-related [7]. The actuarial curves for occurrence of a second primary tumour are presented in Figure 1 (log-rank NS). The 3- and 5-year rates (95% confidence interval) are 18% (12–25%) and 35% (26%–45%) in the etretinate group versus 18% (13%–25%) and 26% (19%–35%) in the placebo

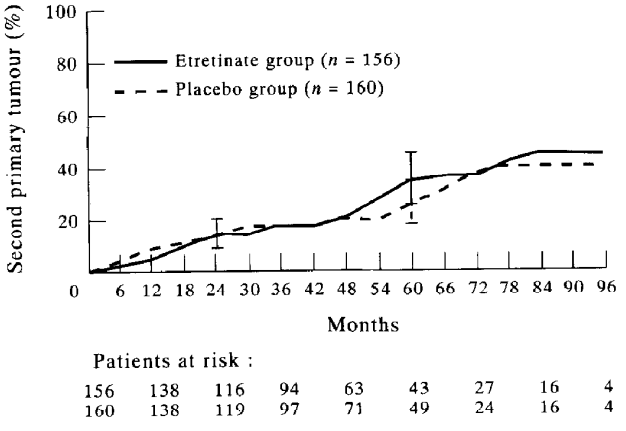

Figure 1. Second primary tumour (95% confidence interval).

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Table 1. Sites of second primary tumours and metastases

	Etretinate ($n = 156$)	Placebo ($n = 160$)
Relapse*	31	20
Local	23	14
Regional	10	9
Metastasis*	21	15
Distant nodes	3	2
Lung and pleura	4	10
Liver	4	2
Bone	8	3
Skin	4	0
Brain	0	1
Other†	3	0
Second primary tumours	42	40
Oesophagus	8	9
Stomach	0	1
Head and neck	18	17
Colon–rectum anal canal	5	2
Lung	7	5
Pancreas	1	0
Bladder	1	2
Skin	0	2
Other‡	2	2

* The total number of events can be superior to the number of patients because of multiple localisations. † Mediastinum, adrenal gland, skin metastasis. ‡ Cholangiocarcinoma and thyroid carcinoma in the etretinate group; prostate carcinoma and hepatocarcinoma in the placebo group.

group. The sites of the second primary tumour are shown in Table 1.

These results are different from those of Hong and associates who used a different retinoid [3]. With a median follow-up of 54.5 months [4] the estimated rates of second primary was 14% in the retinoid group and 31% in the controls (two tailed $P = 0.04$). The percentage of patients with disease progression, either local, regional or distant, was similar in the two groups. It is very likely that this difference in chemoprevention activity between the two products comes from differences in binding to nuclear retinoic acid receptors (RARs) as well as from the modulation of these RARs by the same products [8]. The North American Intergroup study, which opened in 1992, deals with low dose 13-*cis* retinoic acid (30 mg/day), and aims at preventing second primary tumours in patients presenting with early stage head and neck carcinoma: 1000 patients are needed [9]. A joint venture of the EORTC Lung Cancer and Head and Neck Cancer Cooperative Groups was set up in 1988 concerning previously treated squamous cell cancer of the larynx, squamous cell cancer of the oral cavity, or non-small cell lung cancer; four treatment arms are planned in a 2×2 factorial design: retinyl palmitate and *n*-acetyl-cysteine, retinol palmitate, *n*-acetyl cysteine, no treatment [10]. The results of these trials are eagerly awaited to enable physicians to develop effective chemoprevention strategies within the field of cancers of the head and neck.

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"It Feels Better"—Measuring Clinical Benefit

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IN READING the very nice review by Lionetto and colleagues [1] as well as the accompanying article by Van Cutsem and Fevery [2], we are reminded of the devastation caused by pancreatic cancer. The short survival time for the patient is usually accompanied by pain, weight loss and a decline in performance status. Van Cutsem and Fevery call for development of new agents to induce regressions as well as for measures to reduce pain, and to improve both anorexia and quality of life. Indeed, the National Cancer Institute and the Food and Drug Administration of the United States have issued a joint publication indicating that an agent which produces improvement in disease-related symptoms could be approved for use in a particular disease (if the side-effects of the agent did not outweigh the benefit induced by the agent) [3].

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