gression will occur and the chance of curing extracapsularly extending disease will be compromised. The future will probably show that only by curing cancer can the probability of dying from it be decreased; the toxicity of surgery or radiotherapy has decreased in terms of mortality and morbidity of bladder, digestive tract and sexual function. The locoregional therapeutic approach has to remain multidisciplinary between pathologists, urological surgeons and radiation oncologists, using the same criteria of clinical staging, therapeutic evaluation and quality of life, all the more as the diagnosis is made at an earlier stage. Medical information has to be shared with general practitioners to enable patients to have the same perception of their disease. In the future, we need to learn more from the biomolecular approach which could enable us to adapt local and adjuvant treatments according to the tumour phenotype.

1. James ND, Glaholm J. Prostate cancer. What should be studied. *Eur J Cancer* 1995, **31A**, 1565–1566.
2. Menegoz F, Colonna M, Exbrayat C, Mousseau M, Orfeuvre H, Schaerer R. A recent increase in the incidence of prostatic carcinoma in a French population: role of ultrasonography and prostatic specific antigen. *Eur J Cancer* 1995, **31A**, 55–58.
3. Ohori M, Scardino PT. Early detection of prostate cancer: the nature of cancers detected with current diagnosis tests. *Semin Oncol* 1994, **21**, 522–526.
4. Menon M, Parulkar BG, Baker S. Should we treat localized prostate cancer? An opinion. *Urology* 1995, **46**, 607–616.
5. Elgamal A, Van de Voorde W, Van Poppel H, Lauweryns J, Baert L. Selective zonal distribution of tumour volume versus grade in T1c prostate cancer. *J Urol* 1995, **153** (Suppl.), 484A.
6. Bolla M, Van Poppel H. Phase III study of post operative external radiotherapy in pathological stage T3N0 prostatic carcinoma. EORTC protocol number: 22911, activated November 1992.
7. Hanks GE, Corn BW, Lee WR, Hunt M, Hanlon A, Schulteiss TE. External beam irradiation of prostate cancer. Conformal treatment techniques and outcomes for the 1990s. *Cancer* 1995, **75**, 1972–1977.
8. Leibel SA, Zelefsky MJ, Kutcher GJ, *et al.* The biological basis and clinical application of three dimensional conformal external beam radiation therapy in carcinoma of the prostate. *Semin Oncol* 1994, **21**, 580–597.
9. Pilepich MV, Sause WT, Shipley WU, *et al.* Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the radiation therapy oncology group. *Urology* 1995, **45**, 616–623.
10. Pilepich MV, Caplan R, Byhardt RW, *et al.* Phase III trial of androgen suppression using Goserelin in unfavorable prognosis carcinoma of the prostate treated with definitive radiotherapy. *Proceedings of ASCO*, Vol 14, 1995.
11. Bolla M, Gonzalez D, Van Tienhoven G, *et al.* External irradiation and adjuvant hormonal treatment and post-operative irradiation in prostatic carcinoma revisited. Rationale, Trial Design, Eligibility Criteria, Statistical Considerations. In Bolla M, Rambeaud JJ, Vincent F, eds. *Local Prostatic Carcinoma.* Contrib Oncol, Basel, Karger, 1994, Vol. 47, 82–89.
12. Soloway MS, Sharifi R, Wajsman Z, *et al.* Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 prostate cancer. *J Urol* 1995, **154**, 424–428.
13. Van Poppel H, De Ridder D, Elgamal AA, *et al.* Neoadjuvant hormonal therapy before radical prostatectomy decreases the number of positive surgical margins in stage T2 prostate cancer. *J Urol* 1995, **154**, 429–434.
14. Gleave ME, Goldenberg SL, Jones EC, Bruchovsky N, Sullivan LD. Maximal biochemical and pathological downstaging requires 8 months of neoadjuvant hormonal therapy prior to radical prostatectomy. *J Urol* 1995, **153**, 653A.

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Male Breast Cancer: Statistical and Clinical Data for the Maltese Population

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THE MALTESE Islands have a population of approximately 350000 and occupy an area of 316 km^2. They are situated in the centre of the Mediterranean Sea. Data on male breast cancer is very limited and we are not aware of any data ever being presented for Malta [1–3]. Data for this series has been collected through our National Cancer Registry within the department of Health, and is therefore a very reliable source of information. Between 1980 and 1995, a total of 13 male breast cancer cases were diagnosed and registered amongst the male population which stands at 183550, as of the end of 1992.

The crude incidence rate 1990–1995 was 0.8 per 100000. The age-adjusted (World Standard) incidence rate was 0.54 (95% confidence interval 0.44–0.64). The age-adjusted (World Standard) sex ratio, female versus male, was 70.1. The median age at diagnosis was 69 years and it was observed that these rates increased sharply with age. The cumulative risk increased consistently with age (0–74). Thus, in the absence of other causes of death, a male in Malta has an estimated 0.05% risk of developing male breast cancer before the age of 75 years. There was one recorded death in the male population due to breast cancer. The age-adjusted (World Standard) mortality rate was 0.46 per 100000.

Clinically, all these patients were managed on the same lines as adopted for female breast cancer [4–5]. It is quite justified to draw inferences in this way, as the data on this rare tumour is very limited.

All 13 patients underwent a modified radical mastectomy. The histology was reported as being invasive adenocarcinoma in 10 cases and of ductal carcinoma in the remaining 13 cases. For these 13 cases, the pathological staging T of TNM was available; 10 cases were T3 and 3 cases were T1. N was also available; 8 had N1 and 4 cases were N0. There were no cases of distant metastasis at the time of diagnosis. In comparison with other published series, there was no notable variation in pathological findings [6–8].

Among these male breast cancer cases, there was a particular case with a family history of female breast in daughters and sister of the proband [9]. We are now proceeding with more detailed analysis at molecular level, screening DNA for mutations in *TP53, BRCA1* and *BRCA2* in all cases as well as in relatives of the particular case [10].

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1. Sasco JA, Fontaniere B. A population based series of 10 male breast cancer cases. *Eur J Cancer Clin Oncol* 1991, **12**, 1713.
2. Isquierdo MA, Alonso C, Andres LDE, Ojeda B. Male breast cancer: report of 50 cases. *Acta Oncologica* 1994, **33**(7), 767–771.
3. Ciatto S, Iossa A, Bonardi R, Pacini P. Male breast carcinoma: review of a multicentre series of 150 cases. *Tumori* 1990, **76**, 555–558.
4. Wagner JI, Thomas CR, Koh W-J, Rudolph RH. Carcinoma of the male breast: update 1994. *Med Pediatr Oncol* 1995, **24**(2), 123–32.
5. Hecht JR, Winchester DJ. Male breast cancer. *Am J Clin Pathol* 1994, **102** (Suppl. 1), S25–S30.
6. Thomas DB. Breast cancer in men. *Epidemiol Rev* 1993, **15**, 220–231.
7. Sasco AJ, Lowenfels AB, Pasker-De Jong P. Epidemiology of male breast cancer. A meta-analysis of published case control studies and discussion of selected aetiological factors. *Int J Cancer* 1993, **53**, 538–549.
8. Schon M, Zaiac M, Schilag OM. Male breast cancer. *Onkologie* 1995, **18**(1), 16–21.
9. Anelli A, Anelli TFM, Youngson B, Rosen PP, Borgen PI. Mutations of the P53 gene in male breast cancer. *Cancer* 1995, **75**(9), 2233–2238.
10. Thorlacius S, Tryggvadottir L, Olafsdottir GH, *et al.* Linkage to BRCA2 region in hereditory male breast cancer. *Lancet* 1995, **346**, 544–545.

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High-dose Recombinant Interleukin-2/Verapamil Combination in Advanced Cancer

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rIL-2-BASED IMMUNOTHERAPY is a promising approach for patients with advanced melanoma and renal cell carcinoma [1]. IL-2 generates lymphokine-activated killing activity (LAK) by peripheral blood lymphocytes (PBL) which acquire the capacity of MHC-unrestricted killing of tumour cells [2–4]. We have demonstrated that human tumour cell lines, resistant to LAK-cytotoxicity *in vitro*, become sensitive to cytotoxic lymphocytes after 24–48 h exposure to the calcium channel blocker verapamil [5]. Verapamil is active at concentrations (10–100 nM) which can be reached *in vivo* [6]. Therefore, we designed a Phase I clinical study on rIL-2/verapamil combination. After committee approval, written informed consent was obtained from each patient before study entry.

All patients enrolled in the study were given the same verapamil dose, while the dose of rIL-2 given by continuous infusion for 72 h starting day 2 was escalated in the different cohorts of patients (Table 1). Dose escalation was allowed if a minimum of 3 patients had been treated at each dose level of infusional rIL-2 without grade 3–4 toxicities in 2 of 3 patients. Dose escalation over 18 IMU/m^2/day, which can be considered a standard dose [7] and close to the maximum tolerated dose (MTD) [8] of rIL-2 by continuous infusion, was not planned. 10 IMU/m^2/day rIL-2 were given by subcutaneous administration on days 6–10 to all patients who entered the study. Verapamil was administered at the dose of 0.2 mg/kg/h for 3 consecutive days by continuous infusion after a loading bolus dose of 0.15 mg/kg. 18 patients—8 males, 10 females, 10 with malignant melanoma, 7 with renal cell carcinoma, 1 with colon cancer—were enrolled in the study and completed the two planned courses of rIL-2/verapamil. Median age was 49 years (range 22–72). 3 additional patients were treated with 9 IMU/m^2 rIL-2 to further explore the rIL-2 dose which we considered, on the basis of biological activity (see below), as the recommended one for Phase II trials (Table 1).

Grade 1 elevation of BUN and creatinine occurred in 5 patients (28%), respectively, while grade 2 increase of creatinine occurred in 1 patient (6%). Oliguria occurred in 11 patients (61%) and inversion of urine electrolyte in 13 patients (72%). 2 patients experienced grade 2–3 hypotension which resulted in only temporary suspension of therapy. Grade 1 hypotension occurred in 9 patients (50%), but did not result in discontinuation of drug infusion. Synus tachicardia was observed in 7 patients (39%), first degree atrioventricular (AV) heart block in 2 patients (11%), AV dissociation in 1 (6%) and premature ventricular beats in 1. 1 patient had synus bradycardia immediately after bolus verapamil injection which resolved spontaneously with temporary discontinuation of verapamil infusion. Fever occurred in 14 (78%) patients, dyspnoea in 1 (6%), abdominal pain in 13 (72%), anaemia in 10 (56%), nausea and vomiting in 4 (22%), constipation in 4 (22%), increase of serum bilirubin in 5 (28%), diarrhoea in 1 (6%).

We also evaluated the immunomodulatory properties of the rIL-2/verapamil combination by determining the number of circulating eosinophils and induction of cytotoxic activity against the human leukaemia K562 cells. Both peripheral blood lymphocytes cytotoxic activity and circulating eosinophils were maximally increased at the rIL-2 dose of 9 IMU/m^2/day. We observed 1 complete remission in a patient with renal cell carcinoma, lasting 30+ months, and 2 partial remissions (renal cell carcinoma and melanoma), lasting 6 and 9 months. Minor objective responses were recorded in 4 patients (1 with melanoma and 3 with renal cell carcinoma). Disease progressed in 5 patients (Table 1). In conclusion, we demonstrated that a rIL-2 dose of 18 IMU/m^2 could be administered in combination with high-dose verapamil in absence of cumulative toxicity. Furthermore, this combination has biomodulatory properties and antitumour activity and deserves evaluation in Phase II clinical studies.

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1. Rosenberg SA, Lotze MT, Yang J, *et al.* Experience with the use of high dose interleukin-2 in the treatment of 652 cancer patients. *Ann Surg* 1989, **210**, 474–483.