inflammatory carcinoma of the breast with combined modality approach. An update. *Cancer* 1981, **47**, 2537–2542.
30. Buzdar AU, Hortobagyi GN, Montague E, *et al.* Short-term chemotherapy, surgery and radiotherapy in the management of inflammatory breast cancer. *Proc Am Soc Clin Oncol* 1986, 5, 61.
31. Hollender LF, Calderoli H, Bieber S, *et al.* Chimiothérapie pré et post-opératoire deans les cancers inflammatoires du sein. Analyse d'une série de 41 cas. *Chirurgie* 1986, **112**, 84–86.
32. Ackland SP, Bitran JD, Dowlatshahi K. Management of locally advanced and inflammatory carcinoma of the breast. *Surg Gyn Obstet* 1985, **161**, 399–408.
33. Sherry MM, Johnson DH, Page DL, *et al.* Inflammatory carcinoma of the breast. Clinical review and summary of the Vanderbilt experience with multimodality therapy. *Am J Med* 1985, 3, 355–364.
34. Burton V, Cox B, Leight S. Inflammatory breast carcinoma. Effective multimodal approach. *Arch Surg* 1987, **122**, 1329–1332.
35. Leyvraz S, Costa J. Issues in the pathology of sarcomas of the soft tissue and bone. *Sem Oncol* 1989, **16**, 273–280.

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Goserelin Acetate With or Without Flutamide in the Treatment of Patients with Locally Advanced or Metastatic Prostate Cancer

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From March 1987 to December 1990, 373 patients with stage C and D prostate cancer were randomized to receive either goserelin acetate alone or goserelin acetate plus flutamide. At a median follow-up time of 24 months, there was no significant difference in the response rate, progression-free and overall survival between the two treatment groups. In particular, median time to progression was 18 months in the goserelin arm and 24 months in the combined treatment arm ($P = 0.09$). However, median time to progression in stage D patients was 12 months in both treatment groups. Median time to death was 32 and 34 months, respectively. The combination regimen produced a more rapid normalisation of prostatic acid phosphatase levels and a more prompt relief of bone pain. However, significantly more patients in the combination arm experienced treatment-related side-effects such as diarrhoea and increases in transaminase levels. The concurrent use of goserelin acetate and flutamide does not seem to significantly improve the results that can be achieved with goserelin acetate alone.
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INTRODUCTION

HORMONOTHERAPY IS THE most common treatment offered to patients with locally advanced or metastatic prostate cancer. This treatment is beneficial for more than two thirds of patients and induces no significant side-effects. This is particularly true for treatment with luteinizing hormone releasing hormone (LH-RH) analogues that can achieve a chemical castration by interfering with the release of LH at pituitary level. These compounds are well tolerated, require only monthly administration and have been shown to be at least as effective as surgical castration or diethylstilboestrol treatment [1–3]. Therefore, they represent the treatment of choice for prostate cancer patients in many countries.

The main goal of endocrine therapy is to achieve androgen deprivation in order to neutralise androgen stimuli at the prostate cancer cell level. Gonadal ablation, while suppressing most of the circulating levels of testosterone, does not affect adrenal steroidogenesis. Therefore, it is not able to interfere with the biological action of the dihydrotestosterone which is produced at the prostate level through the peripheral metabolic conversion of weak adrenal androgens [4]. For this reason the simultaneous use of gonadal ablation and pure anti-androgens has been suggested [5]. In particular, these investigators reported on the high therapeutic activity of combined treatment with LH-RH analogues and flutamide both in patients with stage D and in those with stage C prostate cancer [6, 7]. In order to test prospectively the therapeutic value of such an approach, an

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international multicentric study, evaluating the value of goserelin acetate alone or in combination with flutamide, was begun in 1986. The results of this study have been published recently [8]. When patient accrual was closed in 1987, a number of institutions belonging to the Italian Prostatic Cancer Project (PONCAP) that were involved in this study, decided to continue with recruitment on their own speculating that a nationwide study might be more appropriate because it would be performed in a more homogeneous group of patients.

PATIENTS AND METHODS

Patient selection

Patients with histological confirmation of cancer and either locally advanced (stage C) or metastatic (stage D) disease were eligible for entry into the trial. Patients previously treated with orchiectomy, hormones or cytotoxic therapy were excluded. Patients were also excluded if performance status was more than 3 (according to UICC score), or life expectancy was less than 3 months. In any case, they were excluded if a strict adherence to treatment and follow-up plan could not be ensured due to geographical movement or co-morbid conditions. Previous radiation to metastatic sites other than those being followed for tumour response was allowed. Similarly, transurethral resection of the prostatic gland was allowed if disease was not confined only to the prostate.

Patients were asked to give a written informed consent to trial entry according to the recommendations of the Committee for the Human Investigations of the National Cancer Institute of Genoa.

Pretreatment assessment, follow-up procedures and response evaluation

Pretreatment evaluation included: complete blood counts and biochemical tests [including serum alkaline and prostatic acid phosphatase (PAP)]; chest radiograph; bone scan and skeletal radiographs of abnormal areas; intravenous pielography; computerised tomographic scan of the pelvis and prostate ultrasonography. Patients were clinically evaluated after the first month of treatment and then every 3 months. Biochemical tests and prostate ultrasonography were repeated with the same frequency, while bone scan, chest X-ray and the other instrumental examinations were repeated every 6 months unless specific symptoms occurred which required their use.

Response to treatment was evaluated according to NPCP-USA criteria [9]. Partial response at the prostate level was defined by a decrease of 50% or more in prostate area (or volume), as assessed through prostate ultrasonography. Centres using transpubic ultrasonography reported on changes in prostate (tumour) area while those using the transrectal technique reported on changes in prostate (tumour) volume.

Bone pain was evaluated by using a four-grade UICC score [10]. Patients' records were reviewed centrally at the coordinating institution by at least two independent clinicians.

Treatment plan

Patients were randomised through telephone contact to receive either goserelin acetate, 3.6 mg subcutaneously every 4 weeks, or goserelin acetate at the same dosage plus flutamide, 250 mg orally three times daily. Flutamide was started concurrently with the first administration of goserelin. Treatment was continued until disease progression or death in all patients. However, flutamide was given at half dosage or temporarily discontinued in patients developing drug-related symptoms. In a few patients flutamide was withdrawn because of toxicity or patient refusal: these patients have been continued on goserelin acetate alone. However, they have been evaluated according to their initial allocation. At disease progression patients receiving goserelin acetate alone were continued on this treatment but were given in addition flutamide, at the same dosage. Progressing patients in the combination treatment arm were treated at the investigator's discretion.

Statistical analysis

Overall survival and progression-free survival were calculated by the product limit method of Kaplan and Meier [11] and the curves were compared using the log-rank test [12]. Calculations were adjusted by disease stage. Overall survival and progression-free survival were measured from the date of randomisation.

Comparisons of response and toxicity between treatments were made by means of the χ^2 test for trend and Fisher's exact test, respectively [13]. All P values correspond to two-sided significance tests.

RESULTS

Between March 87 and December 90, 373 patients were randomised into the study, including the 52 patients entered in the international multicentric study: 186 were allocated to receive goserelin acetate while 187 were given a combination of goserelin acetate and flutamide. The main characteristics of study patients are summarised in Table 1. The two treatment groups were well balanced with respect to major prognostic factors. However, more patients in the goserelin arm had distant metastases at presentation. Median follow-up time was 24 months (range 10–54 months). No significant differences were seen in the response rates of patients receiving the LH-RH

Table 1. Patients' characteristics

	Goserelin (N = 186)	Goserelin + flutamide (N = 187)
Age		
Median	74	73
Range	49–86	48–88
Performance status (UICC)		
0	93 (50.0)	104 (55.6)
1	67 (36.0)	56 (29.9)
2	14 (7.5)	17 (9.1)
3	5 (2.7)	5 (2.7)
Unknown	7 (3.8)	5 (2.7)
Disease stage (AUS)		
C	77 (41.4)	91 (48.7)
D	105 (56.5)	93 (49.8)
Unknown	4 (2.1)	3 (1.5)
Tumour grade		
G1	28 (15.1)	23 (12.3)
G2	88 (47.3)	105 (56.1)
G3	55 (29.5)	46 (24.7)
Unknown	15 (8.1)	13 (6.9)
Elevated PAP	97 (53.3)	85 (46.2)
Bone pain	66 (36.2)	63 (34.2)
Urinary symptoms	127 (68.2)	137 (73.3)

Values are expressed as no. of patients (%).

*Table 2. Best response rate: overall and by disease stage**

	Allocated treatments		
	Goserelin No. (%)	Goserelin + flutamide No. (%)	*P* value
All patients	154	150	
PR	65 (42.2)	79 (52.7)	
SD	52 (33.7)	45 (30.0)	0.06
P	37 (24.1)	26 (17.3)	
Stage C	66	80	
PR	34 (51.5)	48 (60.0)	
SD	30 (45.5)	30 (37.5)	0.32
P	2 (3.0)	2 (2.5)	
Stage D	88	70	
PR	31 (35.2)	31 (44.3)	
SD	22 (25.0)	15 (21.4)	0.30
P	35 (39.8)	24 (34.3)	

*Only charts reviewed centrally were included in this analysis.
PR = Partial response; SD = stable disease; P = progression.

Table 3. Response (%) by disease site in stage D patients

	Prostate		Nodes		Bone	
	G	G+F	G	G+F	G	G+F
PR	35.4	42.0	33.3*	66.7*†	22.3	27.4
SD	53.7	49.3	61.1	27.8	49.2	54.9
P	10.9	8.7	5.6	5.5	28.5	17.7

*CR = 33.3 vs. 55.6%; †*P* = 0.04. G, Goserelin; F, flutamide.

analog alone and of those receiving the combined treatment. However, a trend favoured the latter group in the overall and in any disease stage (Table 2). In addition, significantly more responses were observed in the pelvic lymph nodes in the combined treatment arm (Table 3). A more prompt relief of bone pain (data not shown) and a quicker normalisation of PAP levels, if initially abnormal, were also observed in this treatment group (Fig. 1).

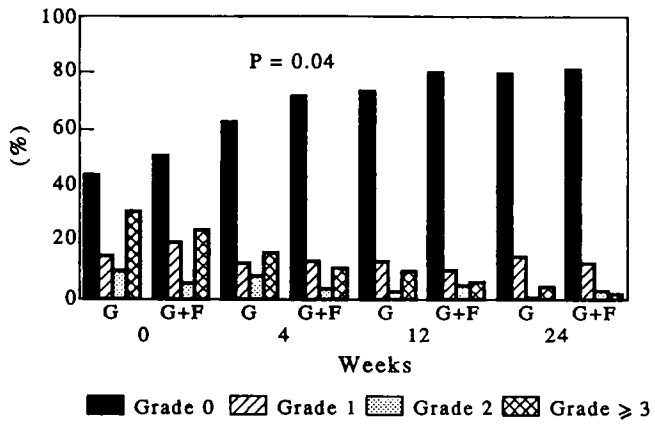

Fig. 1. Behaviour of PAP levels during treatment with goserelin (G) and goserelin plus flutamide (G+F). The levels of PAP were stratified by grades of abnormality: GO = normal value; G1 = less than double normal value; G2 = less than triple normal value; G3 = above triple normal value.

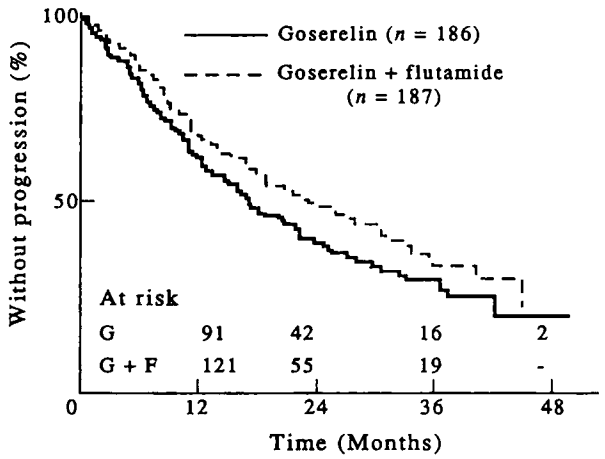

Fig. 2. Progression-free survival. There were 101 observed ever (including death) in the goserelin group vs. 87 in the goserelin pl flutamide group. Median time to disease progression was 18 mont in the goserelin group vs. 24 months in the goserelin plus flutami group (*P* = 0.09).

Table 4 and Figs 2, 3 and 4 show patients' progression-fr and overall survival. A small trend favoured patients treat with goserelin acetate and flutamide with respect to progressio free survival duration (Fig. 2). However, this trend disappear when calculations were adjusted by disease stage (Table 4 Indeed, median time to progression was identical in patien with stage D disease, irrespective of allocated treatment (Fi 3), while a small trend favoured patients with stage C disease the combined treatment group, even though the number events was still very small (Table 4). No difference at all w evident between the two treatment groups with respect to over survival duration (Fig. 4).

Table 5 shows the main differences in drug-related sid effects. Significantly more patients in the combination ar experienced drug-related toxicity, specifically gastrointestin complaints such as diarrhoea and transient or persistent increa in transaminase levels. The incidence of sexual potency loss, h flushes and gynaecomastia was similar in the two treatme groups. In particular, 21% of patients receiving goserelin alo

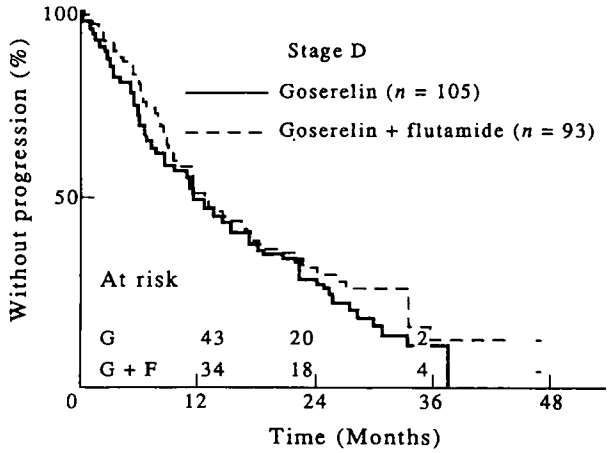

Fig. 3. Progression-free survival of stage D patients. There were observed events in the goserelin group vs. 56 in the goserelin pl flutamide group (*P* = 0.35). Median time to disease progression w 12 months in both groups.

Table 4. Survival and progression-free survival: overall and in any disease stage

	Allocated treatment						
	Goserelin			Goserelin + flutamide			
	No. patients	No. deaths	O/E	No. patients	No. deaths	O/E	*P* value
Survival							
Overall	186	68	1.07	187	62	0.92	0.40
Adjusted for stage	182	68	1.00	184	62	0.99	0.95
Stage C	77	16	1.20	91	16	0.85	0.34
Stage D	105	52	0.95	93	46	1.05	0.64
Progression-free survival							
Overall	186	101	1.12	187	87	0.88	0.09
Adjusted for stage	182	100	1.07	184	87	0.92	0.29
Stage C	77	27	1.07	91	31	0.94	0.60
Stage D	105	73	1.07	93	56	0.91	0.35

O, observed; E, expected.

and 24% of those treated with goserelin and flutamide developed gynaecomastia. No patient treated with goserelin acetate was withdrawn from treatment. 17 patients in the combined treatment group reduced flutamide dose and 21 discontinued this drug.

DISCUSSION

Since the early optimistic reports by Labrie's group [5], a number of studies have prospectively investigated the value of total androgen blockade in patients with advanced prostatic cancer. First generation trials with anandron led to contradictory results [14–16]: the majority of these studies, in fact, were based on relatively small numbers of patients. In addition, Beland's study included a non-random treatment arm [14]. Therefore, none of them is useful in elucidating this issue.

More recently, five large studies have investigated the value of the concurrent use of flutamide and LH-RH analogues [8, 17–19]. Two studies have compared the effectiveness of flutamide plus the slow-release formulation of goserelin acetate to that of goserelin depot alone [8, 17]. In both studies no benefit at all was derived in any disease stage from the simultaneous use of flutamide and goserelin, either in terms of progression-free and overall survival duration, or in terms of objective response rate. However, some improvement in the subjective response rate favoured the patients treated with goserelin and flutamide in the trial of the International Prostate Cancer Study Group (IPCSG) [8].

Our study had a design which was quite superimposable to that of the previous studies: indeed, its design was borrowed from that of the IPCSG trial, as previously described in detail [20]. However, a peculiar feature of our study was the administration of flutamide as second-line treatment to patients initially allocated to goserelin alone.

Present results confirmed those preliminary reported [20] in that they showed no clear-cut benefit favouring the patients receiving concurrent goserelin plus flutamide treatment.

The small progression-free survival advantage in favour of patients in the combined treatment arm can probably be explained by the fact that 10% fewer patients in this treatment arm had distant metastases at presentation. In fact, this advantage disappeared when data were analysed after adjusting for disease stage. In addition, when data were broken down according to this variable, no difference was evident in stage D patients, while only a small, not significant advantage still favoured stage C patients treated with goserelin acetate plus flutamide. In any

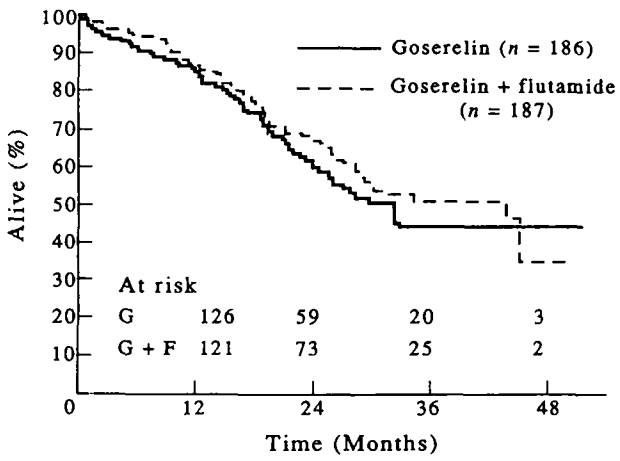

Fig. 4. Overall survival. There were 68 observed deaths in the goserelin group vs. 62 in the goserelin plus flutamide group ($P = 0.40$). Median time to death was 32 months in the goserelin group vs. 34 months in the goserelin plus flutamide group.

Table 5. Side-effects

	Allocated treatments		
	Goserelin (*N* = 154)	Goserelin + flutamide (*N* = 150)	*P* value
Transaminases increase	4 (2.6)	18 (12.0)	0.01
Gastrointestinal toxicity	1 (0.6)	18 (12.0)	0.00
Skin rash	2 (1.2)	5 (3.3)	0.21
Disease flare	5 (3.2)	1 (0.6)	0.11

Only charts reviewed centrally were included in this analysis.
Values are expressed as no. of patients (%).

case, no survival advantage was evident in patients receiving the combined treatment, either in the overall or in any disease stage category. In the present analysis the concurrent use of goserelin acetate and flutamide yielded better results than goserelin alone in terms of objective or subjective response to treatment. In particular, a significant advantage favoured the combined treatment in the response of pelvic nodes. A quicker normalisation of PAP levels, if initially abnormal, was also observed in this treatment group.

It is noteworthy how our results closely resemble those achieved by the international study [8] and how the results of both these studies are in accordance with those of the French study [17]. It is also interesting to note how these trials showed a similar incidence of side-effects in patients receiving the combined treatment, gastrointestinal and hepatic toxicity representing the most common form of flutamide-induced toxicity in all of them. Finally, a similar proportion of patients treated with goserelin alone experienced some form of disease flare in our study and in the IPCSG study (3 and 2.5%, respectively).

No advantage of combined treatment with goserelin acetate and flutamide over surgical orchiectomy was evident in a Danish Cooperative Study, which recruited for the most part patients with distant metastases [19]. Moreover, this study showed that patients initially allocated to orchiectomy had a small (even if not significant) probability of surviving longer than patients treated with goserelin acetate and flutamide, despite the fact that they progressed earlier [18]. Similar results have been achieved in a recent EORTC study that also allocated patients to orchiectomy or combined treatment with goserelin acetate and flutamide [19]. In this study, the advantage of combined treatment with respect to time to progression was even greater. However, again it did not produce increased survival but it did cause a decreased sensitivity to second-line treatment [19]. A more recent analysis of this study seems to disclose a certain survival advantage for patients in the combined treatment arm, specifically for those with "minimal disease" (L. Denis, personal communication). However, no details are available thus far about this more recent analysis. A small advantage in progression-free survival duration favouring the patients treated with goserelin and flutamide also emerged from the meta-analysis of the Danish and EORTC studies [21]. In addition, in both these studies the combined treatment did improve objective response rates in a way that was similar to that observed in our study (about 10% higher response rate).

When only patients with distant metastasis are considered, it is not easy to explain why the same combination treatment with goserelin and flutamide produced some advantage in progression-free survival duration in the Danish and EORTC studies while it did not in the French, IPCSG and PONCAP studies. Indeed, median observation time in all these studies was comparable at the time of publication. This difference might depend upon the different mechanisms of action of surgical castration and LH-RH analogue treatment. LH-RH analogues act not only by inducing a "chemical castration", but they are also supposed to exert a direct antiproliferative effect through their interaction with tumour LH-RH receptors [22]. This additional therapeutic effect might be increased by the concurrent use of a pure anti-androgen which is able to counteract the early agonistic effects induced by these compounds. This effect could be better disclosed by the comparison of goserelin plus flutamide to surgical castration, while it might be blunted by the comparison of combined treatment to goserelin alone.

The results of our study and those of previously mentioned studies contrast with the results of a large intergroup American study that showed a significant increase in progression-free and overall survival for a combination of leuprolide and flutamide compared to leuprolide alone [23]. However, a daily formulation of leuprolide was used in this study and this might provide a less effective control of testosterone secretion than the use of sustained-release formulations, even if no data coming from direct comparison are available in this regard. Should this be true, the concurrent use of flutamide might be more beneficial in patients treated with daily injections rather than in those receiving depot formulations of LH-RH analogues.

In any case, the advantage favouring combined treatment in the American study was achieved with an extra cost in side-effects and was evident mainly in a subgroup of patients which represents only a limited proportion of those with metastatic prostate cancer (no more than 13% of patients with distant metastases in this study).

In conclusion, our results and the majority of those reported in the literature argue against the concurrent use of pure anti-androgens and LH-RH analogues because the small benefit which can be achieved by this approach does not translate into a survival advantage in most patients while it induces a modest but significant increase in side-effects. However, neither our results nor those of the literature rule out that specific patient subsets might benefit from such a combined approach. In particular, Crawford's study and more recently the EORTC study seem to identify patients benefitting from combination treatment as those with distant metastases but "minimal disease". Because a number of studies, including our own, have also enrolled stage C patients, i.e. a group of patients with an even smaller tumour burden, it is possible that some advantage could be drawn from combined treatment in this patient subset as well. However, much longer follow-up is needed to clarify this point, considering that the median survival time of stage C patients is far longer than that of patients with distant metastases.

Finally, additional information about the value of combined treatment will most likely come from the ongoing meta-analysis of trials on total androgen blockade [24].

1. Boccardo F, Decensi A, Guarneri D, *et al.* Long-term results with a long-acting formulation of D-TRP-6 LH-RH in patients with prostate cancer: an Italian Prostatic Cancer Project (PONCAP) study. *The Prostate* 1987, **11**, 243–255.
2. Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *N Engl J Med* 1984, **311**, 1281–1286.
3. Parmar H, Lightman SL, Allen L, Phillips RH, Edwards L, Schally AV. Randomized controlled study of orchiectomy versus long-acting D-TRP6-LH-RH microcapsules in advanced prostatic carcinoma. *Lancet* 1985, ii, 1201–1205.
4. Geller J, Albert JD, Nachtsheim DA, Lozza D. Comparison of prostatic cancer tissue dehydrotestosterone levels at the time of relapse following orchiectomy or estrogen therapy. *J Urol* 1984, **132**, 693–696.
5. Labrie F, Dupont A, Bélanger L, *et al.* Combined treatment with flutamide and (D-Trp6) LHRH ethylamide: fundamental data and 5-year clinical experience. In Giuliani L, Santi L, Boccardo F, Pescatore D, eds. *New Trends in Diagnosis and Treatment of Prostatic Cancer*. Roma, Acta Medica, 1987, 179–207.
6. Labrie F. A new approach in the hormonal treatment of prostate cancer: complete instead of partial blockade of androgens. *Int J Androl* 1984, **7**, 2–25.
7. Dupont A, Labrie F, Giguere M, *et al.* Combination therapy with flutamide and (D-Trp6) LHRH ethylamide for Stage C prostatic carcinoma. *Eur J Cancer Clin Oncol* 1988, **24**, 659–666.
8. Tyrrell CJ, Altwein JE, Klippel F, *et al.* A multicenter randomized trial comparing the luteinizing hormone-releasing hormone ana-

logue goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer. *J Urol* 1991, **146**, 1321–1326.
9. Slack NH, Brady MF, Murphy GP and investigators in the National Prostatic Cancer Project. A reexamination of the stable category for evaluating response in patients with advanced prostate cancer. *Cancer* 1984, **54**, 564–574.
10. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
11. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
12. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, **35**, 1–39.
13. Snedecor GW, Cochran WG. *Statistical Methods*. Ames, Iowa, The Iowa State University Press, 1967.
14. Beland G, Elhilali M, Fradet Y, *et al.* Total androgen blockade for metastatic cancer of the prostate. *Am J Clin Oncol* 1988, **11**, 5187–5190.
15. Brisset JM, Bertagna C, Fiet J, *et al.* Total androgen blockade vs orchiectomy in stage D prostate cancer. Preliminary results of a multicentric French trial. In Giuliani L, Santi L, Boccardo F, Pescatore D, eds. *New Trends in Diagnosis and Treatment of Prostatic Cancer*. Rome, Acta Medica, 1987, 155–166.
16. Navratil H. Double blind study of Anandron versus placebo in stage D2 prostate cancer patients receiving buserelin. In Murphy GP, Khoury S, Kuss R, Chatelain C, Denis L, eds. *Prostate Cancer. Part A: Research, Endocrine Treatment and Histopathology*. New York, Alan R. Liss, 1987, 401–410.
17. Fourcade RO, Cariou G, Coloby P, *et al.* Total androgen blockade with Zoladex plus flutamide vs. Zoladex alone in advanced prostatic carcinoma: interim report of a multicenter, double-blind, placebo-controlled study. *Eur Urol* 1990, **18** (Suppl. 3), 45–47.
18. Iversen P, Christensen MG, Friis E, *et al.* A phase III trial of Zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer* 1990, **66**, 1058–1066.
19. Denis L, Smith P, Carneiro de Moura JL, *et al.* Total androgen ablation: European experience. *Urol Clin North Am* 1991, **18**, 65–73.
20. Boccardo F, Decensi A, Guarneri F, *et al.* Zoladex with or without flutamide in the treatment of locally advanced or metastatic prostate cancer: Interim analysis of an ongoing PONCAP study. *Eur Urol* 1990, **18** (Suppl. 3), 48–53.
21. Iversen P, Suciu S, Sylvester R, Christensen I, Denis L. Zoladex and flutamide vs orchiectomy in the treatment of advanced prostatic cancer. A combined analysis of two European studies EORTC 30853 and DAPROCA 86. *Cancer* 1990, **66**, 1067–1073.
22. Qayum A, Gullick W, Clayton RC, Sikora K, Waxman JB. The effects of gonadotrophin releasing hormone analogues in prostate cancer are mediated through specific tumour receptors. *Br J Cancer* 1990, **62**, 96–99.
23. Crawford ED, Eisenberger MA, McLeod DG, *et al.* A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989, **321**, 419–424.
24. Dalesio O. Complete androgen blockade in prostate cancer. Organizing an overview. *Cancer* 1990, **66**, 1080–1082.

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APPENDIX

The other PONCAP investigators who contributed to this trial include: P. Marchi (I.N.R.C.A., Ancona), A. Reggiani (Arcispedale S. Anna, Ferrara), A. Zanollo (Ospedale Civile, Magenta), M. Pavone Macaluso (Clinica Urologica, Università di Palermo), E. Belgrano (Clinica Urologica, Università di Sassari), M. Ventura (Ospedale S. Andrea, Vercelli), D. Borin (Ospedale Generale, Stradella), F. Micali (Clinica Urologica, Università Tor Vergata, Roma), O. Gazzarini (I.N.R.C.A., Firenze), F. Pisetta (Ospedale Civile, Bolzano), P. Marchetti (Oncologia Clinica, Università dell'Aquila), P. Gallotti (Ospedale Civile, Vigevano), C. Magno (Clinica Urologica, Università di Messina), F. Cicchetti (Ospedale Bassini, Cinisello Balsamo), G. Carbone (Ospedale Garbelli, Catania), C. Giglio (Ospedali Civili, Sestri Levante).

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Central Small Size Breast Cancer: How to Overcome the Problem of Nipple and Areola Involvement

Viviana Galimberti, Stefano Zurrida, Vittorio Zanini, Massimo Callegari, Paolo Veronesi, Salvo Catania, Alberto Luini, Marco Greco and Andrea Grisotti

For centrally located small tumours we have sought, with the aid of a plastic surgeon, to achieve the same radicality as in the other quadrants, while achieving a good cosmetic result. We considered 37 patients with small centrally located breast carcinoma, in whom we performed a new surgical technique. From analysis of this series it emerged that a high percentage (54.1%) had nipple and areolar involvement, suggesting their removal; it is no problem to sacrifice these when a good cosmetic result can be achieved by plastic remodelling.
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INTRODUCTION

CONSERVATIVE SURGERY plus radiotherapy has for some years been the treatment of choice for breast cancers of diameter less than 2.5 cm [1, 2]. Controlled clinical studies with up to 18 years' follow-up have shown that the incidence of local recurrences and of distant metastases after quadrantectomy plus axillary dissection plus radiotherapy (QUART) is similar to that after modified radical mastectomy [3–5]. Furthermore, the indications for conservative treatment, initially reserved for selected cases, have gradually expanded and, when combined